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Thiouracil Treatment in Hyperthyroidism[1]

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IT HAS NOW BEEN well established that the endocrine function of the thyroid gland can be inhibited by the administration of thiouracil. In several species of experimental animals large doses induce a state of hypothyroidism equivalent to that following complete surgical ablation of the gland while in human beings hyperthyroidism is effectively controlled by the continued administration of relatively small amounts (1).

Additional information on the clinical use of thiourea and thiouracil is being obtained and preliminary reports have appeared from several clinics. Himsworth (2) has reported six cases treated successfully with thiourea; Williams and G. Bissell (3) treated nine and Palmer (4) twelve cases with thiouracil and Rawson and his collaborators (5) have used thiouracil to prepare nineteen cases of thyrotoxicosis for surgery. Sloan and Shorr (6) have recorded twelve cases treated with thiouracil and have demonstrated that all of the common metabolic derangements of hyperthyroidism are corrected by this form of treatment. The early development of this subject has been reviewed briefly in several recent articles (7).

The wide use of thiouracil as a routine medical treatment for hyperthyroidism requires that detailed information be available on the optimal dosage, the duration of treatment and the eventual clinical result as well as on the incidence of side effects. The nature of the response in the several clinical types of the disease, the influence thereon of iodine given either before, during, or after thiouracil ther-

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apy and the changes to be anticipated in the degree of thyroid enlargement and in the severity of the exophthalmos should be established.

Observations on the clinical effects of this drug during the past two years have had the aim of providing answers to these questions. In all, 62 persons have been given repeated doses of thiouracil; the distribution of these cases among the several forms of hyperthyroidism is shown in table 1.

TABLE 1. SUMMARY OF CASES TREATED WITH THIOURACIL. THE DOSE IN ALL CASES EXCEPT ONE WAS 0.6 GM. DAILY OR LESS.

Diagnosis	Males	Females	Total
Graves' disease	10	31	41
Toxic nodular goiter	0	8	8
Acromegaly with hyperthyroidism	0	2	2
Total number with hyperthyroidism	10	41	51
Cases with normal thyroid glands	5	6	11
Total number of individuals			62

PRIMARY HYPERTHYROIDISM

Of the 51 cases of hyperthyroidism treated with thiouracil[3] 41 were considered to be examples of Graves' disease—diffuse hyperplastic goiter with hyperthyroidism. Eight of these cases had received iodine shortly before thiouracil was given and these will be discussed later. Those which had not been treated with iodine responded to thiouracil therapy in a fairly uniform manner. In most cases observations were continued during a control period before therapy was begun in order to exclude, as far as possible, the beneficial effects of rest, sedation and reassurance. In some cases determinations of the basal metabolic rate were performed two to six times weekly during the initial period of therapy to determine the rate and extent of the response. In others, treatment was carried out from the out-patient department where observations were usually made at bi-weekly intervals during the first few months.

Rate of the metabolic response. Of the cases of typical Graves' disease which had not previously received iodine, the 10 most satisfactory with respect to frequency of metabolic rate determinations are charted in figure 1. From these data it is possible to form an estimate of the rate of change of the metabolic rate under the influence of thiouracil. The total daily dosages used were 0.3 to 0.6 gm. initially and in most cases this was reduced to 0.2 to 0.4 gm. before the end of the five-week period shown in the figure. These data are quantitatively similar to those published by Rawson and his collaborators (5) who have pointed out the similarity of the metabolic response to thiouracil with the initial response to iodine therapy. It may be noted from figure 1 that the latent period, if any, is short, that the rate falls rapidly during the first two weeks and more slowly thereafter. The plateau which follows the initial response in most of the cases may in some of them be due to a lowering of the dosage but in others it was observed when there was no change in treatment.

It was previously suggested (1) that the chief factors governing the rate at which the metabolism falls to normal under the influence of thiouracil are concerned with the available store of thyroid hormone and the rate of its release from the thyroid gland. It is known

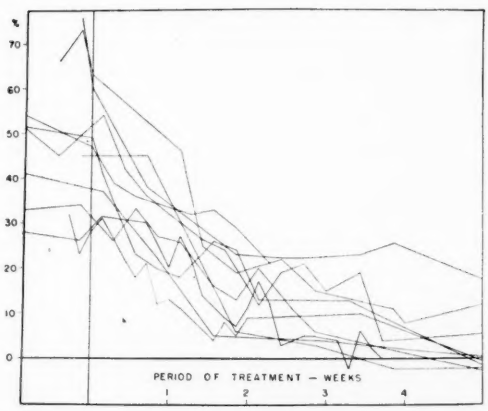

FIG. 1. The rate of the initial response of the basal metabolic rate to the administration of thiouracil in doses of 0.3 to 0.6 gm. daily. The records are from ten selected and previously untreated cases of typical Graves' disease. It may be seen that after the initial fall of the metabolic rate during the first 10 to 14 days, there is in some cases a period of one or two weeks when little further change occurs and then a secondary decline. In all except the two most severe cases the metabolic rate was normal within four weeks. These data are quantitatively similar to those published by Rawson and his collaborators (5).

[3] The thiouracil was supplied by Dr. B. W. Carey of the Lederle Laboratories, Inc., Pearl River, New York.

that thiouracil inhibits the synthesis of new hormone without impairing the activity of that which has already been formed. In Graves' disease the low hormone content of the gland and the rapid rate of its secretion combine to allow a rapid fall in the metabolic rate when thiouracil is given. Conversely, when there is a large store of mobilizable thyroid hormone, as in cases with large nodular goiters, in cases of iodine-treated Graves' disease, and in normal individuals, the rate of response is relatively slow.

Rate of clinical improvement. In the cases to be described, objective clinical evidence of improvement accompanied the fall in the metabolic rate. A decrease in the pulse rate was found to be most valuable as an index when the minimal pulse rates under basal conditions were compared. Of course, a fall to normal of the pulse rate involved a smaller percentage change than the corresponding decrease of the metabolic rate. For example, a fall in the basal metabolic rate from +50 per cent to normal was often accompanied by a decrease in the pulse rate from 100 to 80 per minute. The body weight increased progressively after the initial fall in metabolic rate and usually weight gain continued over many months. Tremor, overactivity, sweating and peripheral vasodilatation usually reverted toward normal as the metabolic rate declined.

Because of the variation in the presenting symptoms it is difficult to say whether symptomatic improvement invariably corresponded with the objective signs of the therapeutic effect. Certain patients claimed to be much improved before there were any changes in the physical signs or laboratory findings. Actually the time of onset of symptomatic improvement was determined by the nature of the most troublesome symptom in the individual case. Irritability, apprehension, and the feeling of tension usually improved early, while improvement in the palpitation, thermophobia, and sweating accompanied the falling metabolic rate. Diarrhea, when present, outlasted the elevated rate of metabolism. Muscular weakness was the last symptom to disappear, and in a number of instances the body weight had returned to normal before muscular strength was completely restored.

The following examples illustrate the course of the response in typical cases. They include respectively: severe thyrotoxicosis with auricular fibrillation, mild hyperthyroidism with paroxysmal fibrillation, thyrotoxicosis complicated by marked muscular atrophy, the complications of anxiety neurosis and of depressive psychosis, and finally the course of therapy in an out-patient.

CASE 1. *Graves' disease, auricular fibrillation.* A man aged 46 years, a plumber by trade, had been well until

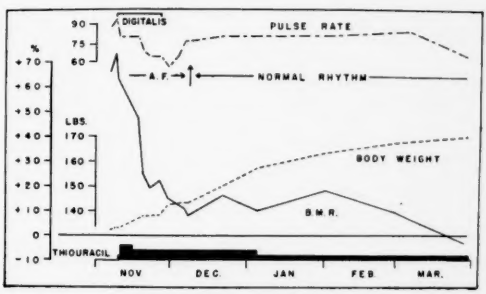

FIG. 2. (Case 1). The influence of thiouracil in daily doses of 0.6, 0.4 and 0.2 gm. upon the course of severe thyrotoxicosis. It will be noted that auricular fibrillation (A. F.) continued until the metabolic rate was nearly normal and then spontaneously ceased.

the spring of 1943. He then noted profuse sweating on the slightest exertion, increased appetite, and shortness of breath while carrying out his normal activities. He found that he readily became exhausted and after a few months his associates remarked on the staring appearance of his eyes. He obtained partial relief of these symptoms by adopting the practise of taking six full meals a day but in spite of the increased diet his body weight decreased from 165 to 132 during nine months. Tremor became incapacitating, double vision developed and he was unable to sleep because of palpitation.

The patient presented all of the classical signs of severe hyperthyroidism. Exophthalmos was striking, the thyroid gland was only moderately enlarged; it was soft and no bruit was audible. The peripheral pulse rate was 95 at rest and totally irregular owing to auricular fibrillation. Metabolic rates before therapy was initiated were +66, +73 and +63 per cent respectively.

The response to treatment is shown in figure 2. A total daily dose of 0.6 gm. of thiouracil for 5 days was followed by a dose of 0.4 gm. for the next seven weeks and 0.2 gm. thereafter. Full doses of digitalis were given and maintenance doses continued for a total of 19 days. Thirteen days after treatment was begun the metabolic rate was +19. Two weeks later the cardiac rhythm reverted to normal although no quinidine was given. The symptoms cleared rapidly.

After a period of 32 days in the hospital the patient returned home and two weeks later resumed his trade. While the metabolic rate remained slightly elevated for three months, weight gain was progressive, and by the end of five months he had gained 37 pounds.

The thyroid gland showed no appreciable change in size during the period of treatment. It appeared to be softer and more difficult to delineate but the fullness of the neck indicated that no great decrease in size had taken place. A bruit was never heard. During the first six months of observation, little change in the degree of exophthalmos was noticeable. The diplopia from fatigue of the muscles of convergence quickly improved and the staring appearance became less striking although there was a slight increase in the degree of proptosis.

CASE 2. *Questionable Graves' disease, paroxysmal auricular fibrillation.* A man aged 66 had noted weakness and some loss of weight for a period of one year and had suffered from symptoms typical of peptic ulcer for twenty years. During the three months before admission to the hospital he lost 15 pounds in weight. His appetite was fair, but bowel movements had become frequent and his mood had changed to one of agitation and irritability. He complained of a dislike of warm weather and a tendency to sweat excessively. The thyroid gland was not enlarged and the eyes were normal. The skin was not abnormally warm, flushed or moist. Paroxysms of auricular fibrillation occurred at irregular intervals during the month of hospitalization. Basal metabolic rates were +18, +12, and +13. During periods of normal cardiac rhythm the basal pulse rate varied between 64 and 88, and the circulation time (decholin) was 22 seconds. Serum cholesterol determinations showed values of 264 and 270 mg. per 100 cc. He was treated with sedatives, digitalis, belladonna and quinidine without relief. Thiouracil was given in a dose of 0.6 gm. daily for 25 days followed by 0.2 gm. daily thereafter. During the first three weeks of thiouracil therapy there was no clinical improvement and metabolic rates varied between +4 and +28. During the sixth week of thiouracil administration, two weeks after returning home, the cardiac symptoms disappeared. At nine weeks the metabolic rate was found to be −13 per cent, he was completely free of symptoms and all medication except thiouracil was discontinued. The metabolic rate remained subnormal, reaching a minimum of −18 per cent during the fifth month. Having been free of all cardiac and gastric symptoms for seven months and having gained 26 pounds he discontinued thiouracil after a total of nine months' treatment.

CASE 3. *Graves' disease, eunuchoidism, muscular atrophy.* A man aged 50 years, a mill worker, was well until five years before admission to the hospital. He then was troubled by pains in the joints of the extremities, which seemed to fluctuate in intensity with the weather. His physician treated him for rheumatism. During two months before admission to the hospital he was obliged to remain at home because of weakness. The body weight fell from 144 to 118 pounds. While he had always liked cold weather he now found that he had become most intolerant of heat and sweated readily. There were attacks of palpitation, shortness of breath, swelling of the ankles at night and sleeplessness. The appetite failed.

The most striking finding was an advanced atrophy of the muscles, especially those of the shoulder girdle and upper arms and thighs, suggesting some form of primary muscular atrophy. There was no exophthalmos, the thyroid was not perceptibly enlarged and no bruit could be heard. The testes were small and the external genitalia hypoplastic. The metabolic rate was moderately elevated, the serum cholesterol was 175 mg. per 100 cc. and the circulation time (decholin), 9 seconds. The course of this patient during therapy is shown in figure 3. The metabolic rate fell quickly to normal and tachycardia was controlled following the administration of 0.6 gm. of thiouracil daily. There was a distinct increase in strength at the end of one month of treatment but only after the body weight was nearly normal could normal activities be resumed. After five and one-half months of treatment the patient was symptomatically well. Although the metabolic rate had been maintained between −8 and −2, the facial expression and slowness of speech and actions suggested early myxedema. Treatment was discontinued. One month later the metabolic rate was +9, and he had lost 5½ pounds in weight and the puffiness of the face had disappeared. Because of the possibility that the hyperthyroid state was still present treatment with 0.2 gm. of thiouracil daily was resumed. Although the state of eunuchoidism remained unaffected, complete restoration of strength and muscular development occurred without the administration of androgen.

FIG. 3. (Case 3). A prompt effect of thiouracil (0.6 gm. daily) upon the pulse rate and basal metabolic rate in a case of hyperthyroidism with advanced muscular atrophy. A daily dose of 0.2 gm. was adequate for maintenance.

CASE 4. *Graves' disease, anxiety neurosis.* A girl aged 19 complained of nervousness of several years' duration. At 18 an enlargement of the neck was noted; this caused worry and was thought responsible for increasing nervousness and irritability. Other common symptoms of hyperthyroidism had not been noticed. The patient was admitted to the hospital

because of marked agitation. She was irritable, startled by her surroundings, and unable to sit still. The thyroid gland was enlarged to about four times the normal size and over it there was a thrill and a bruit. The basal pulse rate varied from 100 to 112. The skin was warm but not abnormally moist. Three B. M. R. determinations before treatment were +52, +49 and +41. Thiouracil was given in a dose of 0.2 gm. every twelve hours. Seven days later the B. M. R. was +18 and the basal pulse 80, and 38 days after initiation of treatment the B. M. R. was −6 and the basal pulse 76. The patient felt well and was less active and apprehensive. Remaining symptoms of anxiety were interpreted as evidence of an anxiety neurosis. The thyroid gland did not change perceptibly in size and the thrill and bruit persisted. A maintenance dose of 0.2 gm. of thiouracil daily was continued.

CASE 5. *Graves' disease, depressive psychosis.* During the course of one year a 48-year-old woman developed a profound mental depression requiring admission to a state institution. At the beginning of the year the patient was nervous and apprehensive; she found that the behavior of her family and friends irritated her excessively and finally she was unable to endure their association. Later on she withdrew from all personal contacts and would not respond to questions or commands. She complained also of muscular weakness, fatigue, feverishness, irregular menstrual periods and double vision. Upon admission to the psychopathic hospital it was observed that although she sat immobile and completely unresponsive, perspiration dripped from her face. Two weeks later, at the time of transfer to a general hospital, typical signs of Graves' disease could be detected. There was a marked stare and slight proptosis. However the thyroid was not detectably enlarged and there was no audible bruit. The basal metabolic rates, determined with some difficulty, were +22, +24, +31 and +52 per cent. Thiouracil was given in a dose of 0.6 gm. daily. In seven days the metabolic rate was +8 and in twenty-one days −12 per cent. The dosage was reduced to 0.2 and later to 0.1 gm. daily and the low metabolic rates were maintained. The psychosis improved markedly; stilbestrol 0.3 mg. daily was given with the aim of relieving any concomitant menopausal symptoms and within one month of dismissal the patient returned to work. The only residual evidence of the psychosis consisted of a paranoid tendency and an over-compensation in the direction of a belligerent attitude; she talked volubly and appeared unnaturally self-confident. Thiouracil therapy was continued for seven months. This patient has remained well for three months without further medication.

CASE 6. *Graves' disease, hypertension, glycosuria.* A woman aged 56 was seen in the out-patient department one month after the onset of unusual nervousness, apprehension, tremor and inability to sleep. The patient was obese and had a mild degree of hypertension; the urine contained sugar. Treatment with diet and insulin was continued for six weeks but the glycosuria remained unaltered and 17 pounds of weight were lost. The persistent symptoms and the observations of slight thyroid enlargement, widened palpebral fissures, tremor, sweating and nervousness led to the diagnosis of hyperthyroidism. The metabolic rate was sustained at +45 during a subsequent control period of two weeks. Thiouracil was then given in a dose of 0.1 gm. three times daily after meals. All symptoms were relieved by the end of one month and as may be seen from figure 4 the response of the metabolic rate, pulse rate and extent of weight gain

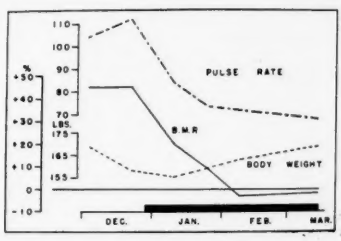

FIG. 4. (Case 6). Determinations of the pulse rate, basal metabolic rate and body weight illustrate the effect of the administration of thiouracil (0.1 gm. three times daily) on the course of Graves' disease complicated by congestive heart failure.

were consistent with a prompt control of the thyrotoxic state. The thyroid gland did not enlarge perceptibly and no bruit was audible; the stare decreased. The patient was subsequently maintained with a dose of 0.1 gm. of thiouracil twice daily.

Changes in the goiter. Observations on the size, consistency and signs of increased vascularity of the thyroid gland were made at frequent intervals. While accurate measurements of these local changes could not be quantitatively precise, some of the changes were definite. It was found that during drug treatment the glands usually became softer. This is the reverse of the well-known effect of iodine. It is not surprising therefore that the most marked decrease in firmness was seen in the cases with indurated glands, including those previously treated with iodine. The unusual softness of the thyroid gland often created the impression that a decrease in size had occurred; the edges and borders of the thyroid previously so easily felt became indistinct and the gland's extent seemed to blend into the soft tissues of the neck. In several instances glands which had been estimated as two to three times the normal size could no longer be palpated after one to three months of treatment. Usually, however, a fullness persisted at the base of the

neck which indicated that an enlarged thyroid was still present even though it could not be outlined by palpitation.

In cases which exhibited large goiters before treatment, changes in the size of the gland were more easily observed. An unquestionable enlargement occurred in several instances during the first few months of therapy. Some of the patients noted this fact. Others expressed the belief that their goiters were smaller, presumably because they were more impressed by the smoother contours of the neck than by the overall fullness of the thyroid region.

In most cases enlargement of the thyroid was not an impressive finding during the course of therapy. This is contrary to expectation, for it was the goitrogenic effect of such compounds as thiouracil that led to their introduction into therapeutics. Several factors may possibly explain the infrequent occurrence of gross thyroid enlargement in patients with Graves' disease treated with thiouracil. In the first instance the dose used clinically is much lower on a body weight basis than that required in animals to induce myxedema or cretinism and considerably lower than that required to induce a maximal enlargement of the thyroid gland. It has been shown in rats that doses which markedly lower the iodine content of the thyroid gland are much below those needed to induce thyroid enlargement. It is possible that the clinical dosage, especially the maintenance dose, corresponds more closely to the low dosage required to induce a partial failure to thyroid hormone synthesis, rather than to the dosage levels needed for the total inhibition which results in the more striking compensatory thyroid enlargement.

A second explanation is related to the degree of hypothyroidism induced. Thyroid size is largely controlled by the activity of the thyrotropic hormone. In Graves' disease the thyroid gland from its size, structure and vascularity appears often to be under the influence of nearly maximal thyrotropic stimulation. It is conceivable that a partial inhibition of the excessive thyroid hormone production does not serve as an added stimulus to thyrotropin production and consequently does not induce further stimulation of the already hyperplastic thyroid gland. Observations on some of the treated cases suggest that gross thyroid enlargement is apt to occur if the basal metabolic rate is maintained at subnormal levels by the prolonged administration of a dose in excess of the minimal requirement.

Alterations in the intensity of the bruit and thrill were most readily observed in cases which initially exhibited signs of increased vascularity of the thyroid. While in several cases no detectable change occurred during the first two to three months of treatment, in three cases an increase in the bruit and thrill accompanying an increase in the size of the gland occurred during the early weeks of treatment. In only one instance did a definite bruit develop during treatment. The most consistent finding was the eventual disappearance of the signs of increased vascularity. This therefore may well prove to be a valuable index of the progress of therapy and its significance is discussed below in connection with the occurence of remissions.

The two cases of Graves' disease which exhibited the largest goiters and which illustrate the influence of thiouracil treatment upon the size and vascularity of the gland are recorded below. These two cases also illustrate the striking effect of iodine administered for a short period during the course of thiouracil therapy.

CASE 7. *Graves' disease with large goiter, induced myxedema.* A 40-year-old woman, the mother of three children, had previously been well although somewhat overactive and nervous. In the spring of 1943 the patient contracted a streptococcal pharyngitis which was treated with full doses of sulfadiazine in another hospital. This episode was followed by progressive weakness, muscle pain, tremor, palpitation, weight loss and exophthalmos. The thyroid gland had been enlarged for some years; it was now three to four times normal in size, quite firm and smooth and a loud bruit was audible over it.

The subsequent course of this patient's illness is shown in figure 5. During the sixteen-day period of hospitalization the patient received 0.1 gm. of thiouracil every eight hours. The basal metabolic rate fell from +40 to +10, the basal pulse rate declined from about 105 to 90 and the patient's symptoms regressed. On the day of discharge from the hospital the thiouracil dosage was reduced to 0.1 gm. twice daily. Two weeks later symptoms had returned and the basal metabolic rate had increased to +29. Following an increase in the dosage of thiouracil to 0.3 and later to 0.4 gm. daily, all symptoms except local ones related to the enlarging thyroid gland again disappeared. During the third and fourth months of treatment it was apparent that although the metabolic rate was

subnormal the thyroid gland was becoming larger. The bruit was louder and a thrill was palpable over the lateral lobes and isthmus of the gland. This was accompanied by an uncomfortable sensation of fullness in the neck. Thiouracil was continued in a dose of 0.3 gm. daily and Lugol's solution 3 drops daily was given. Ten days after the initiation of iodine therapy the metabolic rate was found to be −25 per cent and a striking change in the thyroid gland was noted. The gland was distinctly smaller and the loud bruit and forceful thrill had entirely disappeared. Though the dose of thiouracil was reduced to 0.2 gm. daily and the iodine solution to two and later to one drop daily the metabolic rate remained low and signs and symptoms of myxedema appeared. The patient became lethargic, moved, thought and spoke slowly. She complained of an inability to concentrate or to use a pen or typewriter or to play the piano because of stiffness of the fingers. The face became pallid and puffy, considerable hair was lost from the scalp. The skin was dry and papery and tightly stretched. Both thiouracil and iodine were therefore discontinued. Thirteen days later the metabolic rate had increased from −27 to +2 per cent, nine pounds of weight had been lost, and all symptoms of myxedema had disappeared. Thiouracil was resumed in a dose of 0.2 gm. daily, reduced five weeks later to 0.15 gm. and after a further period of five weeks to 0.1 gm. daily. The metabolic rate remained within normal limits and the patient was free of symptoms. A moderately loud bruit returned temporarily following the resumption of thiouracil treatment. The size of the gland steadily decreased. After eight months of treatment thiouracil was discontinued; the thyroid gland was still large, approximately of the size it had been before treatment, the patient was entirely free of symptoms and the body weight was normal.

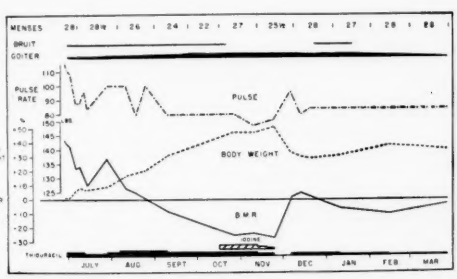

FIG. 5. (Case 7). The effects of thiouracil and Lugol's solution on the size and degree of vascularity of the thyroid gland and on the pulse rate, body weight and basal metabolic rate in Graves' disease. The maximal dose of thiouracil was 0.4 gm. daily.

Within two weeks of cessation of treatment there was subjective evidence of an elevated metabolic rate and thiouracil was resumed in a dose of 0.2 gm. daily. Five days later the metabolic rate was +10 and the body weight had decreased from 140 to 137½ pounds. The symptoms were quickly controlled and thiouracil treatment was continued.

CASE 8. *Graves' disease with large goiter.* A woman of 50 who had always lived in the neighborhood of Boston had had a noticeable goiter for many years. The mother had had a goiter and died at 43 of an undiagnosed illness and a sister had recently been operated on for thyrotoxicosis. Seven years prior to the present illness the patient noted an enlargement of the goiter accompanied by symptoms of nervousness and fatigability. Six months before admission to the

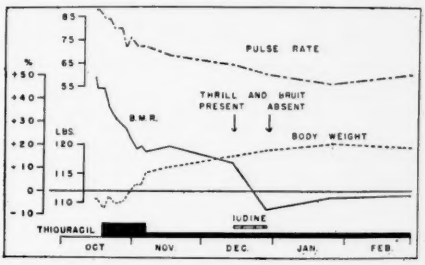

FIG. 6. (Case 8). The effect of iodine administered during the course of thiouracil therapy in a case of Graves' disease with an unusually large goiter. The dose of thiouracil was 0.6 gm. followed by 0.2 gm. daily.

hospital these symptoms became severe and progressive. In spite of a ravenous appetite there was a weight loss of 18 pounds. The patient exhibited all the signs of long-standing hyperthyroidism together with minimal exophthalmos and striking lid retraction. The thyroid gland was five to six times normal in size and had a pronounced thrill and a loud bruit. Metabolic rates were +49 to +44, the basal pulse 88 and the circulation time (decholin), 9 seconds.

As shown in figure 6, thiouracil was given in a dose of 0.6 gm. daily for 19 days. During this interval the basal pulse rate fell to 72, and the metabolic rate to +17. The patient was dismissed from the hospital while not yet entirely free of symptoms. She continued to take thiouracil in a dose of 0.2 gm. daily at home. After five weeks she felt entirely well and had regained her normal weight. However the metabolic rate was found to be +12, the skin was still warm and moist, the patient was noticeably hyperactive and nervous. In view of these findings and because of the persistence of a loud bruit and distinct thrill over the thyroid gland iodine was given. Two drops of Lugol's solution were taken daily for two weeks. In this short period the metabolic rate fell to −8 per cent, the thyroid gland became smaller and the signs of hyperemia, previously so striking, had become undetectable.

A maintenance dose of 0.2 gm. thiouracil was continued for a further period of four months. The basal pulse rate remained slow, the body weight and metabolic rate remained normal, the patient felt well. The thyroid gland decreased in size but developed an audible bruit. Medication was continued.

Effect of added iodine. It is apparent that in

these two cases the administration of iodine during the course of thiouracil therapy was followed by the same type of response as is observed when iodine is given to cases of untreated Graves' disease. The metabolic rate fell, even though in one case it was already subnormal. The thyroid gland decreased in size, became firmer, and all signs of increased vascularity disappeared. The mechanism of the phenomenon, like that of the action of iodine in untreated Graves' disease, remains obscure.

These observations indicate that small doses of iodine may be useful in the management of certain cases of Graves' disease treated with thiouracil. Whether most cases would do better with added iodine is not known. When thiouracil is used as a pre-operative medication the increased softness and hyperemia of the gland sometimes make the surgical procedure more difficult. Iodine may prove to be useful in quickly reversing this surgical difficulty if partial thyroidectomy is contemplated. It should be pointed out, however, that iodine tends to cause a storage of hormone in the thyroid gland. As the clinical dosage of thiouracil is one which does not completely block the formation of thyroid hormone, the prolonged administration of iodine may permit the accumulation of appreciable amounts of hormone within the gland even when maintenance doses of thiouracil are being given. Consequently the continued administration of iodine may serve to counteract the desirable features of thiouracil as a pre-operative medicament.

In the following case the metabolic response suggests that iodine may cause the storage of thyroid hormone in the gland during thiouracil therapy.

CASE 9. *Graves' disease, congestive heart failure, auricular fibrillation.* A 46-year-old woman had suffered from symptoms of mild congestive heart failure for 8 years. A new set of symptoms appeared six months before admission to the hospital; the patient became irritable and exhibited outbursts of anger and weeping. She became tired easily, felt uncomfortably warm, and perspired freely. During three months there was a 40-pound weight loss. For the following three months there was a gain of 21 pounds accompanying further progression of symptoms and the development of edema. At the time of admission to the hospital the patient was obviously suffering from heart failure. There was dyspnea at rest, edema of the feet and legs, enlargement of the liver, evidence of pulmonary edema, and auricular fibrillation. The thyroid was four to five times the normal size and there was a definite bruit over the gland. The metabolic rate was +48 per cent and the basal pulse 88. Digitalis and mercurial diuretics were given. Thiouracil was started in a dose of 0.6 gm. daily and twenty-four hours later Lugol's solution, 30 drops per day, was started. Within one week the edema had cleared, 10 pounds of weight had been lost and the basal metabolic rate had fallen to +18. In nine days it was +12. At the time that iodine was discontinued the metabolic rate ceased to fall and remained between +11 and +19 per cent for four weeks. It then declined to −5 and −6 per cent and was maintained at that level by a daily intake of 0.2 gm. of thiouracil. Several trials with quinidine with and without digitalis failed to cause the cardiac rhythm to revert to normal. However when the metabolic rate had reached −6 and digitalis alone was being given the cardiac rhythm reverted to normal. The patient has since remained symptom free on no medication except thiouracil.

Cases pretreated with iodine. Eight of the cases of Graves' disease had been treated with iodine before thiouracil was administered. The extent to which the thiouracil response was modified depended in part upon the duration of the iodine therapy. In two cases full doses of iodine had been administered for many months before thiouracil was begun and in these the metabolic rate had remained high in spite of the iodine and there was a much delayed response to thiouracil therapy. A third received iodine for 12 days and experienced a moderate degree of improvement. When the iodine was discontinued and thiouracil substituted there was initially a return of symptoms and a sustained rise in the metabolic rate; only after 46 days was the disease controlled. Another case responded in much the same way when thiouracil was substituted for iodine. In figure 7 data on three of these cases are compared with those of three cases of toxic adenoma and with a composite curve of the metabolic response of ten cases of Graves' disease.

CASE 10. *Iodine-refractory Graves' disease.* An English woman aged 61 had escaped to Canada from her home in France in 1939. Shortly thereafter she was troubled by nervousness and a moderate loss of weight. In January 1942 she developed lobar pneumonia while visiting in California. Following a prompt recovery, the body weight which had fallen to 93 pounds from a normal of 122 was not regained. Weakness persisted and the eyes became prominent. Treatment with Lugol's solution was followed by improvement. During the following year and one-half several

exacerbations of the symptoms occurred, although iodine was continued.

Upon admission to the hospital the patient weighed 88½ pounds. There was a marked stare, a moderate degree of exophthalmos, a rapid pulse and a loud systolic murmur could be heard over the entire precordium. The thyroid gland was diffusely enlarged and very firm but not nodular. Thiouracil was given in a total daily dose of 0.3 gm. At the end of 18 days of treatment there had been no change in the metabolic rate and only a slight improvement in the clinical condition. The patient returned to Canada and continued to take thiouracil in a dose of 0.1 gm. three times daily. At the end of seven weeks the dose was

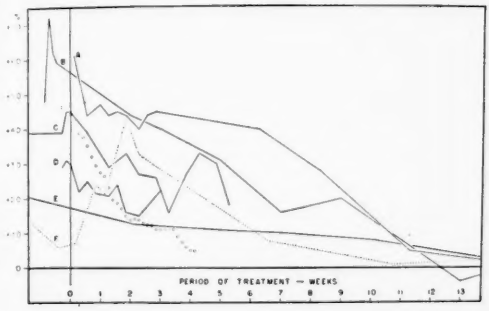

FIG. 7. Slow metabolic responses in six patients compared with the composite curve (open circles) of the ten cases of Graves' disease shown in figure 1. Curves A and B refer to cases 10 and 11 respectively which had previously been treated with iodine for long periods. Curves C, D and E refer to cases 13, 14 and 15 respectively, examples of toxic nodular goiter and curve F (base 12) shows the result of discontinuing a brief course of iodine coincident with the initiation of thiouracil therapy.

reduced to 0.1 gm. twice daily though no metabolic response had occurred. Not until the eleventh week of treatment did the metabolic rate reach normal (curve A, Fig. 7). Thiouracil was continued for a total of eight months. The patient remained in good health, regained her normal weight and was eventually able to play eighteen holes of golf each day. No change in her condition was noticeable during the ensuing three months since thiouracil was discontinued.

CASE 11. *Graves' disease uncontrolled by iodine.* A man aged 54 suffered from a streptococcal pharyngitis in April, 1941. Complete recovery followed sulfonamide therapy. Seven months later the infection recurred and was treated in a similar manner. The pharyngitis was controlled but the patient did not recover his normal health. At this time a son entered the armed forces and caused the patient to suffer unusual anxiety. There soon followed progressive weakness, tremor, sweating and extensive muscle wasting accompanied by a weight loss totalling 38 pounds. His physician treated him with Lugol's solution and sedatives for a period of eight months during which the progress of the disease became less rapid but the patient did not improve. Iodine therapy was continued until he entered the hospital.

The initial metabolic rates on the four consecutive days following iodine withdrawal were +52, +76, +61 and +59. The pulse was rapid but regular, and the skin was flushed and moist. The palpebral fissures were wide but there was no exophthalmos. The thyroid was moderately enlarged; no bruit was audible. The patient refused to stay in the hospital because of pressing business affairs and was therefore treated from the out-patient department. A dose of 0.2 gm. thiouracil was taken three times daily for the first five weeks, and twice daily for the next four. The metabolic response of this patient is shown in curve B of figure 7 from which it may be seen that some seven to eleven weeks were required before normal values were reached. A maintenance dose of 0.1 gm. twice daily was taken for four months and then thiouracil was discontinued. During the six and one-half months of treatment the patient gained 32 pounds. Symptoms largely disappeared when his metabolic rate approached normal but weakness, particularly of the legs, accompanied by pain in the atrophic muscles persisted until his body weight approached normal. Four weeks after thiouracil therapy was stopped the metabolic rate was +25 per cent and six weeks after, +40 per cent. Although symptoms of hyperthyroidism were minimal, thiouracil treatment was reinstituted.

CASE 12. *Graves' disease, iodine and thiouracil treatment.* A woman of 59 complained of ill health since the death of her husband two years previously. Easy fatigue was the most prominent symptom until two months before admission to the hospital when there developed increasingly severe attacks of palpitation and shortness of breath. The patient exhibited but little evidence of hyperthyroidism. The basal pulse rate varied between 80 and 96, the eyes were somewhat prominent, and there was a slight diffuse enlargement of the thyroid gland. Metabolic rates were +20, +30 and +16. When Lugol's solution was given for 12 days the metabolic rate fell to +6. This response was accompanied by a slowing of the pulse and by a considerable subjective improvement. The iodine therapy was then discontinued and thiouracil begun in a total daily dose of 0.6 gm. whereupon there was a prompt elevation of the metabolic rate which reached a maximum of +43 in 12 days. Symptoms returned and were of greater severity than before treatment. As shown in curve F of figure 7, the metabolic rate subsequently fell to a level of +2 eleven weeks after thiouracil had been started. After a total of five months of treatment thiouracil was discontinued.

In two further cases, pretreated with iodine, the response to thiouracil appeared to be definitely delayed but in these instances observations were not made at sufficiently frequent intervals to define the extent of the delay.

Two other cases received iodine under different circumstances and in them the response was prompt. One of these entered the hospital in diabetic coma complicated by lobar pneumonia. There was clear evidence of severe thyrotoxicosis which had apparently recently reoccurred, a subtotal thyroidectomy having been performed seven years previously. In addition to specific measures for the control of the diabetes and pulmonary infection, potassium iodide was given intravenously and Lugol's solution administered daily thereafter. On the fifth and sixth day, after a pronounced clinical improvement had occurred, the basal metabolic rates were found to be +49 and +51 per cent. Thiouracil was begun in a dose of 0.4 gm. daily and the iodine continued for a further 9 days. After stopping the iodine the metabolic rate continued to fall rapidly and was 0 on the twenty-third day of thiouracil therapy.

Presumably in this instance the 6 days of iodine treatment in the course of severe hyperthyroidism did not permit the accumulation of an amount of hormone within the gland sufficient to delay appreciably the subsequent thiouracil response.

In the second instance a young woman suffering from Addison's disease was treated with iodine for a mild degree of thyrotoxicosis. After 14 days of iodine therapy the metabolic rate had fallen from an average of +11 per cent to −8 per cent. Thiouracil, 0.6 gm. daily, was given and the iodine continued for a further 12 days when the metabolic rate was −15 per cent. Two weeks after the iodine was stopped the rate was again found to be −15 per cent and the thiouracil was reduced to 0.3 gm. and later to 0.2 gm., a dose which maintained the low level of metabolism satisfactorily. After three months, a temporary cessation of thiouracil therapy resulted in the return of elevated metabolic rates and treatment was resumed. In this case the prior administration of iodine had no influence on the thiouracil effect but the reason for this exceptional behavior is not apparent.

Exophthalmos. In the majority of the cases reported here accurate measurements of the degree of ocular protrusion were not made during the course of therapy; small changes in the degree of exophthalmos were consequently not detected. In nearly every case the degree of exophthalmos appeared to decrease during the early months of treatment and this was noted by the patients and their friends as well. A part of this change was undoubtedly due to a decrease in lid retraction which would diminish the degree of stare. Improved strength of the extra-ocular muscles and increase in the subcutaneous fat of the face would also lessen the subjective and objective impressions of proptosis. In most cases, however, the degree of improvement in the appearance of the eyes was such as to suggest that the extent of the exophthalmos did actually decrease. In some, the eyes were normal within six months while in others improvement was not convincing until six months or more had elapsed. In one instance of striking exophthalmos (*Case 20* below) there was no definite change during the course of one year's observation although the patient had a normal metabolic rate during this period.

Only one case, thus far, has exhibited a distinct increase in the degree of exophthalmos during treatment. *Case 1* above had a moderate degree of proptosis, accompanied by marked lid retraction and weakness of the extra-ocular muscles. Two months after treatment was started the appearance of the eyes had improved and there was no further difficulty of convergence and no complaint of double vision. During the fourth month the patient complained of a burning sensation in the eyes; the conjunctivae were reddened and the exophthalmos appeared to have increased.

It is of interest to recall in connection with the theories of origin of exophthalmos, that the administration of thiouracil induces a compensatory increase in the secretion of thyrotropic hormone from the pituitary. This indirect stimulus to thyrotropin secretion is probably not as great as that of thyroidectomy, at least not with the usual clinical doses of the drug. Were the thyrotropic hormone a major etiologic factor in exophthalmos one would expect a high incidence of this complication following either thyroidectomy or thiouracil administration and this is apparently not the case either in human beings or in experimental animals.

Whatever the etiology of exophthalmos,

there is no evidence from the clinical results to date indicating that this complication will be made more severe by the use of thiouracil.

TOXIC NODULAR GOITER

Relatively few cases of toxic nodular goiter or toxic adenoma have been treated with thiouracil alone. Only eight cases have been observed and five of these were eventually thyroidectomized. In two, treated for only 10 and 24 days respectively, no appreciable metabolic response occurred. In the six others there was a considerable delay before the metabolic rate declined. Three of these, illustrated in figure 7 are described:

CASE 13. *Toxic nodular goiter.* A 68-year-old Irish woman had had a large goiter for many years. She entered the hospital because of weight loss, nervousness, tremor and weakness. These symptoms had been noted intermittently for a period of five years and during that period there were intervals of perfectly normal health. It was subsequently established that for many years the patient had been treated inadvertently with iodine administered in the form of tablets of potassium iodide as a cough remedy. The patient was found to be mildly thyrotoxic. There were no detectable ocular signs. The thyroid gland was about six times the normal size and appeared to extend into the thorax, where a large diffusely calcified nodular gland was demonstrated by x-ray. Thiouracil was given as a pre-operative medication 0.6 gm. daily for one week and 0.4 gm. daily thereafter. As shown in curve C of figure 7 the metabolic response was definite but slow. Lugol's solution was added during the third to sixth week of treatment but this did not accelerate the response. Subtotal thyroidectomy was carried out at the end of six weeks of this combined therapy.

CASE 14. *Toxic adenoma.* A 57-year-old woman was known to have had a goiter on the right side of the neck for 15 years. She was free of definite symptoms of thyrotoxicosis until two months before admission to the hospital, when she experienced attacks of palpitation and profuse perspiration. The patient became nervous, irritable, worried a good deal and was unable to sleep. Diarrhea developed but the appetite was unimpaired. In the hospital the patient appeared to be mildly hyperthyroid. The eyes were normal. In the thyroid gland there was a single round mass about 4 cm. in diameter. It was smooth and firm and over it a systolic bruit was audible. The metabolic rates on three consecutive days were +29, +31 and +30 per cent respectively. Thiouracil was given in a dose of 0.4 gm. daily. The metabolic response was slow but definite, as shown in curve D of figure 7. A subtotal thyroidectomy was performed during the fourth week of treatment.

CASE 15. *Toxic adenoma.* A 60-year-old woman had experienced symptoms of mild hyperthyroidism for two years. For three months she had found it an effort to continue her work in a laundry because of fatigue, shortness of breath and palpitation. She ate heartily but lost five pounds in weight. The thyroid gland was found to be irregularly enlarged by numerous rounded nodules one half to two centimeters in diameter. No bruit was audible in any area. According to the patient's statement her neck, which was full and misshapen by the goiter, had not changed in appearance in recent years. The patient appeared to be markedly thyrotoxic, she was hyperactive, nervous and apprehensive, there was a marked tremor of the hands and fingers, the skin was warm and the palms moist. The blood pressure averaged 195/80 and the basal pulse 100. Three metabolic rate determinations at weekly intervals showed +21, +15 and +22 respectively. Thiouracil was given in a dose of 0.1 gm. twice daily and the patient continued to carry on her work. During the next two months as shown in curve E of figure 7 there was little change in the metabolic rate, the values being +13, +11, +10 and +8 per cent respectively and there was little change in the clinical condition of the patient. The dosage of thiouracil was then increased to 0.1 gm. three times daily and during the third and fourth months of treatment a definite clinical improvement was noted. The patient gained weight, became tired less readily, was quiet and composed, and felt well. The metabolic rate fell to +2 and the pulse rate averaged 80 at rest. No change could be detected in the goiter and no bruit could be heard. The eyes exhibited none of the usual signs of Graves' disease.

The delayed response of patients with large adenomatous glands is thus quite similar to that of cases of Graves' disease which have been treated for long periods with iodine. The usual histological appearance of toxic nodular goiters suggest that some portions of the gland are overactive and deficient in stored hormone while others are less active and filled with dense hormone-containing colloid. It is possible that these latter areas provide the large supply of hormone which sustains the high metabolic levels observed during the early weeks of thiouracil treatment.

ACROMEGALY

Two cases of hyperthyroidism occurring as a part of the syndrome of acromegaly have been treated with thiouracil. The course of one of these patients was as follows:

CASE 16. *Hyperthyroidism, acromegaly, heart failure.* A woman 47 years old had had no menstrual periods since the age of 19 years. At 39, enlargement

of the fingers and face and a change in facial expression were first noted. Shortly thereafter the patient was found to have an elevated blood pressure. Two years before admission to the hospital symptoms of congestive heart failure became incapacitating. Hyperthyroidism was detected and a subtotal thyroidectomy was performed. Within a few months the metabolic rate was again found to be markedly elevated and a course of roentgen irradiations to the pituitary region was given without any effect on the hyperthyroidism, acromegaly or heart failure.

The patient presented the typical physical changes associated with acromegaly, the heart was very much enlarged and the signs of a severe degree of cardiac failure were present. The basal metabolic rates after two months of bed rest were +63, +64 and +64 during the week prior to the initiation of thiouracil therapy. A chart of the metabolic rates during the administration of 0.6 gm. of thiouracil daily showed a regular decline to +18 in four weeks. During the first three weeks of treatment the edema increased and required the administration of diuretics at more frequent intervals. Thereafter the condition improved and the patient returned home. During the next six months the dosage of thiouracil was varied from 0.2 to 0.4 gm. daily. Occasional metabolic rate determinations yielded values between +10 and +29 per cent, the higher rates following periods when the thiouracil was given in a daily dosage of 0.2 gm.

Symptomatic improvement continued during this interval but eventually edema became severe, shortness of breath, palpitation and precordial pain progressed and the patient was readmitted to the hospital. Though the dosage of thiouracil had been increased to 0.5 gm. daily the metabolic rates during the next three weeks varied between +6 and +16 per cent. The cardiac failure progressed rapidly and the patient died, presumably in ventricular fibrillation. The heart was found to weigh one kilogram. There was gross splanchnomegaly. A large chromophobe adenoma was found in the region of the sella turcica. The thyroid gland weighed 27 grams, although a radical bilateral resection had been done eleven months previously. The gland was mildly hyperplastic and somewhat nodular; in many areas the acini were large and filled with dense colloid. The iodine concentrations of two random blocks of tissue were found to be respectively 36.6 and 44.2 mg. per 100 gm. of fresh tissue. These values are only slightly lower than normal.

The second case of acromegaly was similar with respect to the degree of hypertension and congestive heart failure. The signs of acromegaly and of hyperthyroidism were less marked. After a period of bed rest and before specific treatment was started the metabolic rates decreased to between +14 and +20 per cent, a degree of elevation which might have been due to the heart failure. However, readings as high as +45 per cent had been obtained at intervals prior to this, and thiouracil therapy was therefore instituted. During the course of eight months there were several short periods when treatment was interrupted but for most of that period a dose of 0.3 to 0.6 gm. of thiouracil was taken daily. At no time during treatment did the metabolic rate fall to normal and there was no change in the degree of heart failure and no clinical improvement.

The reason for the failure to obtain a metabolic response in this case is not clear. Even assuming that the diagnosis of hyperthyroidism was incorrect it was expected that continued treatment would eventually lower the metabolic rate. It is possible that the rate of oxygen consumption was determined largely by the state of heart failure or by some other metabolic stimulus, and that the thyroid gland contributed little to the increased metabolic rate.

In the first case the metabolic rate was markedly lowered by thiouracil but was not reduced to normal or subnormal levels even though large doses were given. This might also suggest that some other metabolic stimulus was responsible for a major part of the oxygen consumed. On the other hand the iodine concentration in this gland was found to be but little lowered after many months of treatment, suggesting that there had not been an effective inhibition of the synthesis of thyroid hormone.

INDUCED MYXEDEMA

It was apparent from the first treated case that the continued administration of compounds of this type would eventually reduce the metabolic rate to subnormal levels unless the dosage was appropriately adjusted when the basal metabolism approached normal.

Impending hypothyroidism was often indicated by the patients' symptoms and by the general appearance and behavior before the metabolic rate became subnormal. Symptoms of myxedema are presumably due to a lack of thyroid hormone in the tissues rather than to the low rate of oxygen consumption. It would appear, therefore, that there is a delay in the lowering of the metabolic rate after the quantity of thyroid hormone in the body has been reduced.

The dosage which resulted in detectable changes of early myxedema varied somewhat in different patients. *Case 7* was given 0.4 gm. of thiouracil daily for four and one-half months when the metabolic rate reached −22 per cent. The basal metabolic rate in *Case 19* reached −15 per cent when a dose of 0.1 gm. was being taken after a total of six months of treatment. The other cases which showed evidence of subnormal thyroid function were given dosages intermediate between these two extremes.

It would seem to be important for several reasons to avoid this complication. The state of hypothyroidism is uncomfortable to the patient, it increases the likelihood of thyroid enlargement and the unnecessarily large dosages of thiouracil increase the possibility of toxic side effects. In every case, thus far, the metabolic rate rose to normal when the dosage was reduced or temporarily omitted.

The ready induction of hypothyroidism in cases of Graves' disease is in contrast with the difficulty encountered in lowering the metabolic rate of normal individuals.

EFFECT UPON THE NORMAL THYROID

Only a few observations have been made on the effect of thiouracil in individuals with normal thyroid glands. The results are outlined here to show that prolonged treatment is necessary to induce a lowering of the metabolic rate. The eleven persons treated received 0.4 or 0.6 gm. daily in divided doses. In six cases treated for less than 42 days there was no effect upon the basal metabolic rate, pulse rate or body weight and no detectable change in the thyroid gland. Two cases of advanced heart failure were treated for 52 and 60 days respectively. Toward the end of the period of treatment there was a slight lowering of the metabolic rate but no other clinical evidence of an effect. One patient at the end of 93 days of treatment showed no conclusive evidence of hypothyroidism, while the last case, treated continuously for many months showed a marked fall in the basal metabolic rate, enlargement of the thyroid and evidence of impending myxedema after five months of treatment.

It is apparent that the induction of myxedema in individuals with normal thyroid glands is not a very practical procedure; the time required is obviously long and it may be that when myxedema is eventually induced troublesome enlargement of the thyroid gland will occur as it did in the one case mentioned above.

Several factors possibly contribute to the long latent period. The normal thyroid contains a large store of hormone all of which is apparently available for release. It may be estimated that a gland weighing 15 grams would contain an amount of hormone equivalent to about 5 grams of desiccated thyroid. As a daily dose of 150 to 200 milligrams of thyroid powder by mouth is required to maintain a normal metabolic rate in myxedematous subjects, one might estimate that the equivalent of 100 to 150 milligrams would be the approximate daily output by the thyroid gland *in situ*. Thus the normal gland would appear to contain sufficient hormone to maintain a normal rate of secretion for 33 to 50 days. As the clinical dosage of thiouracil is considerably lower, proportionately, than the dose required in animals to induce complete thyroid inhibition, it is reasonable to suppose that thyroid hormone synthesis could proceed at a slow rate when a dose of 0.4 to 0.6 gm. is given to normal persons. This factor would add appreciably to the time required to free the thyroid gland of its stored hormone as a certain small fraction is constantly being added. A number of factors are known to influence the rate of thyroid hormone secretion and these may be expected to modify further the latent period. Increased environmental temperature, starvation and illness decrease the rate of hormone liberation and one might expect that such inactive glands may become depleted of hormone more slowly than would the glands of healthy, active individuals in cooler environments. In view of these considerations it is to be expected that individuals with normal thyroid glands would not develop hypothyroidism until thiouracil had been given for a period of time to be counted in months and which might vary widely in different persons.

TOXICITY

An estimate of the incidence of side effects from the administration of thiouracil can be made from an analysis of the data on all per-

sons treated with the drug. In all there have been 62 cases: 11 with normal thyroid function and 51 cases of hyperthyroidism. In several instances it was difficult to judge whether untoward symptoms were caused by the drug or whether they had some other basis. The most serious complication was the one previously reported case of agranulocytosis which was almost surely attributable to thiouracil in an excessive dose of 2 gm. daily. This patient recovered and it is of interest to note that although no history of allergic manifestations

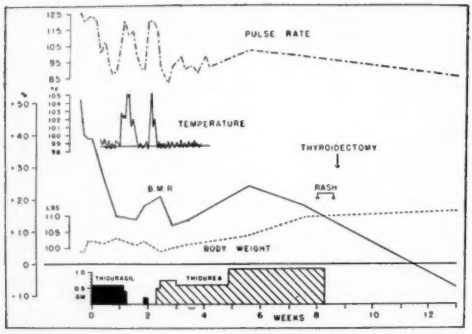

FIG. 8. (Case 17). The occurrence of fever during the course of thiouracil therapy. The fever quickly subsided when the drug was withdrawn and returned when a single dose of 0.2 gm. was administered. A dose of 1.2 gm. of thiourea was necessary to control the disease and this resulted in the appearance of a skin rash.

could be obtained he subsequently experienced a febrile reaction to sulfathiazole and a scarlatiniform eruption following the administration of phenobarbital. It is possible therefore that individuals who readily develop allergic reactions may be more apt to become sensitized to thiouracil.

One further case of marked leukopenia occurred during the administration of thiouracil. In this instance thiouracil was given in a daily dose of 0.6 gm. for 62 days and 0.3 gm. for a further 31 days with the aim of inducing hypothyroidism as an adjunct to the treatment of cardiac failure. On the 85th day a streptococcal infection of the finger developed following a cut and was quickly followed by a spreading lymphangitis and lymphadenitis. The patient did not return to the clinic until a week later and in that interval she received 4 gm. of sulfamerizine daily for 3 days and 3 gm. daily thereafter. On admission the total white cell count was 2000 per cu. mm. of which 5 per cent were granulocytes. Cessation of both drugs, local treatment of the digital infection and of the ulcerative stomatitis and pharyngitis were quickly followed by complete recovery; the number of granulocytes increased daily and the differential count became normal within 10 days.

It was impossible to determine in this case to what degree thiouracil, sulfamerizine, and the infection, respectively, contributed to the leukopenia. Had this patient been under more careful observation the complication might probably have been detected before reaching an alarming degree of severity.

In the two following cases febrile reactions occurred which were shown to be due to thiouracil by the subsequent administration of test doses.

CASE 17. *Graves' disease, sensitivity to thiouracil and thiourea.* A young woman aged 23 had been unduly nervous and irritable for two years. For about one year there had been noted a steady progression of weakness, shortness of breath and tremor. The eyes became prominent. Shortly before medical advice was sought the symptoms became incapacitating; the patient was continuously thirsty, passed large volumes of urine, ate ravenously and developed diarrhea. Palpitation disturbed sleep and nine pounds of weight were lost in a month. Two older brothers had experienced similar episodes in their early twenties and had been successfully treated by partial thyroidectomy. The patient had had no other serious illnesses but was inclined to develop skin rashes attributed to certain foods.

In the hospital the patient exhibited the typical signs of Graves' disease. There was pronounced exophthalmos and the thyroid gland was diffusely enlarged to about four times the normal size. Over the gland a strong thrill and low bruit were noted. The basal pulse rates varied from 120 to 128 and the basal metabolic rates during the first four days of bed rest were +51, +40, +39 and +39 per cent respectively. The subsequent course of this patient's disease is outlined in figure 8. Six days after the initiation of thiouracil in a dose of 0.2 gm. three times daily the metabolic rate had fallen to +15 and the basal pulse to 88. On the ninth day of treatment the temperature, which had been elevated slightly since admission to the hospital, suddenly rose to 102.8°F. and on the next day to 105.2°F. Repeated physical and laboratory examinations failed to reveal a cause for the fever. Thiouracil was therefore discontinued. Thirty-six hours after the last dose of thiouracil the temperature was normal. Three days later a single dose of 0.2 gm. thiouracil was

given at 7 A.M. Oral temperatures taken at hourly intervals remained normal until 4 P.M., when an elevation began which reached 105.2° twelve hours after the administration of the drug. This reaction was interpreted as drug fever. Thiourea was then given in place of thiouracil and the patient was allowed to return home. As shown in figure 8 the initial treatment with 0.8 or 0.6 gm. of this compound permitted a rise in the metabolic rate to +24 and a quickening of the pulse; symptoms of hyperthyroidism returned. When 1.2 gm. of thiourea was given for the next three weeks the symptoms were controlled; there was a moderate fall in the metabolic rate, a gain in weight, and a slowing of the pulse. Just as recovery appeared to be progressing satisfactorily a widely distributed morbilliform rash appeared. As this resembled eruptions previously encountered with thiourea it was recommended that thyroidectomy be performed. At operation 27.5 grams of thyroid tissue was removed. Microscopic sections showed wide areas of markedly hyperplastic colloid-free tissue separated by more normal regions. Total iodine determinations on two blocks of tissue showed the very low concentration of 2.5 mg. per 100 gm. wet weight.

CASE 18. *Graves' disease, auricular fibrillation, drug fever.* A woman of 54 dated the onset of her disease back fourteen months to the day when her son entered the armed forces. Worry and anxiety at that time were accompanied by an increased appetite. Some months later the eyes were noted to be prominent, thirst and increased frequency of urination became troublesome and bowel movements were frequent. During the six months prior to admission to the hospital the patient suffered from frequent attacks of palpitation, precordial pain and dyspnea. She was unable to carry out any muscular effort without discomfort and finally pain in the right upper abdomen and swelling of the feet and ankles were observed. Four days before admission the patient developed an upper respiratory infection and an x-ray plate of the chest revealed an area suggestive of pneumonia or pulmonary congestion.

The signs of hyperthyroidism were characteristic. The skin was hot and moist in spite of a normal rectal temperature. Auricular fibrillation was present and there was evidence of cardiac decompensation. The eyes were prominent but not frankly exophthalmic. The thyroid gland was only slightly enlarged and no bruit was heard. The area of density in the lung was interpreted as one of atelectasis.

The clinical course of this patient is charted in figure 9. Following digitalization, thiouracil in an initial dose of 0.6 to 0.4 gm. was administered for 11 days. The metabolic rate fell from the initial levels of +76 and +56 per cent to +27 during this period and the pulse rate showed corresponding slowing. There was a considerable loss of edema fluid and a fall in body weight. Fever appeared on the ninth day and reached 104.8°F. on the tenth. It was accompanied by no localizing signs of infection and no rash. Thiouracil was discontinued and the temperature was normal one day later. After the temperature had been normal for 48 hours thiouracil was given in doses of 0.025, 0.05, 0.1 and 0.2 gm. at twelve hour intervals. Shortly after the last dose the patient felt cold and the temperature rose to 103°F. No further thiouracil was given until two days later when it was resumed in doses of 0.025, 0.05, 0.1 gm. at twenty-four hour intervals; two doses of 0.2 gm. were then given in one day. Hourly temperature readings during this period showed a maximal elevation to 99°F. While the patient gave no evidence of further sensitivity to the

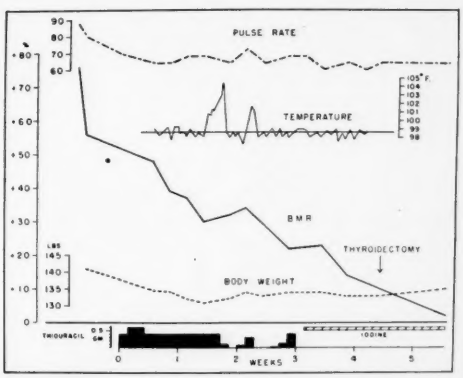

FIG. 9. (Case 18). Apparent desensitization in a case of drug fever from thiouracil. The metabolic rate continued to fall when iodine was given in the place of thiouracil.

drug it was considered advisable to discontinue it. Iodine was given in full doses and a partial thyroidectomy was performed. In spite of the untoward reactions to the thiouracil the metabolic rate fell steadily and continued to fall when iodine was substituted.

Two further cases of fever have been encountered and while they were not proven to be due to the drug, it is highly probable that the thiouracil given was responsible for the fever.

It is apparent, therefore, that of the 61 cases treated, 5 or 6 showed major toxic effects—an incidence of about 10 per cent. Each of these reactions came early in the course of thiouracil administration and thus far there has been no evidence of chronic toxicity. Other instances of toxic reaction have been reported (3, 6, 8).

Mild side-effects, not with certainty attributable to thiouracil, have included one case of intractable diarrhea, and several instances of leukopenia of varying degree. Although the total leukocyte count has fallen to 3,000 or

4,000 on some occasions, it subsequently rose in spite of the fact that the drug was continued. It is apparently a common observation that the white cell count is sometimes low in cases of hyperthyroidism, and it is uncertain whether or not all of these mild leukopenias were caused by the drug.

TABLE 2. TIME REQUIRED FOR DEFINITE SYMPTOMS AND SIGNS OF HYPERTHYROIDISM TO RETURN WHEN THIOURACIL WAS DISCONTINUED BEFORE A REMISSION HAD OCCURRED

Case No.	Period of Continuous Treatment	Period of Normal Metabolism Under Treatment	Interval Before a Return of Hyperthyroidism
	days	days	days
17	9	0	18
21	105	14	32
19	37	23	40
22	53	45	45
23	68	68	30
24	94	80	45
11	217	131	28
3	165	151	28
7	241	150	10

On the basis of the observations made thus far it would seem that the best indications of impending danger of toxic reactions are the subjective sensations of the patient and the body temperature. Frequent leukocyte counts, while helpful, apparently are not as reliable as clinical symptoms in indicating the early onset of serious complications. Serious side-effects could probably be avoided if the patients were instructed to seek medical advice as soon as abnormal symptoms are experienced.

REMISSION

It was clear from the first experiments with thiourea and thiouracil that hyperthyroidism could be controlled with these agents for as long as treatment was continued. When therapy was withdrawn after a short period, the metabolic rate rose and symptoms returned. It was thought that a more prolonged period of treatment would be conducive to the occurrence of a true remission. To obtain information on the requisite duration of treatment and on the incidence of remission during therapy, it is necessary that the drug be discontinued and frequent observations made over a prolonged period of time thereafter. From the nature of the action of thiouracil one would expect that an overproduction of thyroid hormone would follow within a few days of stopping the drug, if the cause of the disease were still in operation; within a few weeks the increased thyroid activity should be clinically apparent and detectable by determinations of the metabolic rate.

In the absence of any evidence of a return of the disease after two months or more it must be concluded that some change in the endocrine systems has taken place which has permitted the patient to return to a normal physiologic state. It is not known what pathologic changes cause hyperthyroidism and it is therefore impossible to say whether thiouracil treatment modifies the cause of thyrotoxicosis. It is possible, however, that the disturbing effects of hyperthyroidism contribute to the maintenance of the disease, and that only if thiouracil is continued long enough will it provide a sufficient interval during which recovery can take place.

Thus far thiouracil medication has been discontinued in 18 cases. In nine the cessation of treatment after relatively short periods was followed by a prompt return of symptoms. The data on these cases, outlined in table 2, show that treatment for as long as 151 days was followed by a prompt return of symptoms when medication was discontinued. The figures given in the table for the interval between the cessation of therapy and the return of hyperthyroidism are maximal values. Had observations been made more frequently, the rising metabolism could have been detected sooner in most cases; the maximal free interval of 45 days is an overestimate. In some of these cases the

TABLE 3. DURATION OF TREATMENT IN CASES WHICH EXPERIENCED AN APPARENT REMISSION DURING THERAPY

Case No.	Period of Continuous Treatment	Duration of Normal Metabolism During Treatment
	mos.	mos.
19	6½	6
25	9	8½
20	6½	6
10	8	5½
5	6½	6
26	7½	7
27	8½	8
12	8	6
2	9	8

course of treatment was not without complications; in *Case 7*, for example, a period of myxedema intervened requiring a brief lapse in treatment.

True remissions during therapy apparently occurred in 9 cases. In these, therapy was continuous for periods of six and one-half to nine months and normal metabolic rates were maintained for five and one-half to eight months. The fact that no symptoms and no clinical or laboratory evidence of a return of the disease followed within a period of two to nine months has been taken as evidence that a remission has occurred. It is still too soon to say that these cases represent true cures and there are no data to indicate the incidence of recurrence or the duration of remission.

Two of the first cases of remission are as follows:

CASE 19. *Recurrent Graves' disease, lasting remission.* A 43-year-old woman had been thyroidectomized three years previously for thyrotoxicosis and had suffered a recurrence of symptoms shortly thereafter. The initial response to therapy with thiouracil was reported previously (1). From February until early September, 1943, as shown in figure 10, thiouracil was given in a dose of 0.2 to 0.05 gm. daily. The weight gain was satisfactory, the metabolic rate remained at normal or slightly subnormal levels and the patient was free of symptoms. Treatment was discontinued in September, 1943 and to date there has been no rise in the metabolic rate. The body weight

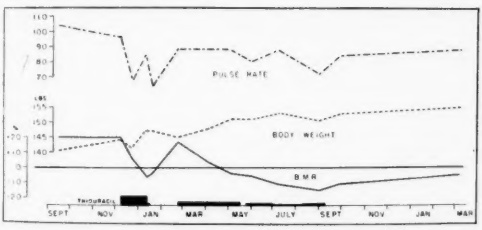

FIG. 10. (Case 19). Lasting remission after six and one-half months of continuous thiouracil therapy. The maintenance dose was varied between 0.2 and 0.05 gm. per day.

has been maintained and no symptoms or signs of a return of hyperthyroidism have been noted. The thyroid gland was not palpable and at no time could a bruit be heard.

CASE 20. *Graves' disease, lasting remission.* A 32-year-old man had noted that he was not in normal health for a period of one year. In carrying out his duties as a fireman he noted that an emergency call to activity would tire him long before the task was completed. During the year the body weight declined from 158 to 130 pounds. The eyes became prominent and tired easily. Shortness of breath, palpitation, thermophobia and sweating became incapacitating and the patient entered the hospital in a state of exhaustion.

There was exophthalmos to a marked degree. The thyroid gland was slightly and diffusely enlarged and a distinct bruit was audible. The pulse was rapid but regular and a systolic murmur of moderate intensity

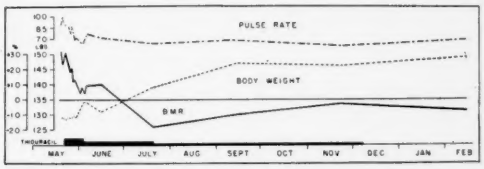

FIG. 11. (Case 20). Changes in the pulse rate, body weight and basal metabolic rate during and after the administration of thiouracil. The initial response to 0.3 gm. daily was prompt and the maintenance dose was reduced to 0.1 gm. daily to avoid hypothyroidism. The patient remained well when treatment was discontinued.

was audible over the precordium. The skin was warm and flushed. Perspiration was profuse in a room which was comfortably warm to the examiner. Daily metabolic rates were +32, +23, +28 and +31 before thiouracil treatment. The drug was given in a dose of 0.2 gm. twice daily and, as may be seen from figure 11, the metabolic response was prompt. Determinations of the metabolic rate were made each day, and within 48 hours of starting the drug the metabolic response began and levels of about +5 were reached in 10 days. A similar decrease in the pulse rate occurred and the weight gain was rapid. Two weeks after returning home the patient was able to resume his duties with the fire department. A total daily dose of 0.2 gm. was continued for seven weeks, after which the metabolic rate was found to be −18 per cent. This low rate of metabolism was not accompanied by any symptoms or signs suggestive of myxedema and even when the dosage of thiouracil was further reduced to 0.1 gm. once daily subnormal metabolic levels were maintained. After nearly seven months of treatment, thiouracil was discontinued. Careful observations over the ensuing five months have failed to show any evidence of a return of the disease. The only detectable residuum is a prominence of the eyes. It is estimated that no change in the degree of proptosis has occurred.

It would be most helpful to be able to determine when treatment could safely be omitted. Premature interruption of therapy might be expected to delay the anticipated remission, but there is as yet no other way of finding out whether treatment is still required. It is possi-

ble that some prognostic significance can be attached to the changes in the size and vascularity of the thyroid gland. *Case 8* above at the end of the six and one-half months of treatment exhibited a loud thyroid bruit and pulsatile thrill. As the metabolic rate was within normal limits under the influence of only 0.2 gm. of thiouracil daily it was presumed that this was not a manifestation of the goitrogenic effect of the drug but rather an indication of the persistence of the etiologic basis of the disease. Whether this interpretation was correct or not is not known, but the treatment was continued. In *Case 7* the bruit had been absent for a period of two and one-half months and normal metabolic rates had continued although the daily dosage had been reduced to 0.1 gm. Treatment was then discontinued, only to be followed by a return of symptoms within 10 days. In *Cases 25* and *27* the gland had decreased in size and the bruit was known to have disappeared more than three months before treatment was stopped; and in these instances there was no return of the disease. Unfortunately changes in the size of the gland and in the bruit in the other cases treated for long periods were either not sufficiently clear, or were not observed carefully enough to permit an analysis.

COMMENT

The cases used in this study were largely unselected and were representative of the types of hyperthyroidism encountered in this part of the United States. Large nodular goiters were not common and most of the cases were of the Graves' type. Of the 51 cases of hyperthyroidism, 41 were female. In other parts of the world particularly in goitrous regions a larger proportion of cases with toxic nodular goiter would doubtless have been encountered. The slower response of such cases and the frequency of essential surgical procedures would have made the study less satisfactory.

On the basis of this limited experience final conclusions on the optimal method of treatment for thyrotoxicosis are not possible. However certain suggestions may be helpful to those seeking further experience with this drug. The most suitable cases for this form of chemotherapy are those of primary hyperthyroidism of any degree of severity and particularly those whose thyroid glands are not excessively large. In such patients the response is prompt, all symptoms can be controlled for indefinite periods, and the incidence of spontaneous remissions is probably high. There would seem to be no cause to use surgery in these cases. Patients with hyperthyroidism and large nodular goiter are not as quickly controlled. Many of these respond poorly to iodine; thiouracil is effective if given for a long enough time. Surgery may be required if the possibility of malignant neoplasm is likely or if the size of the gland is troublesome for local or cosmetic reasons. From the observations made it would appear that the artificial induction of myxedema in normal individuals is not a practical procedure because of the long period of latency and the possibility of stimulating the development of a goiter.

The question of accessory therapeutic procedures can probably be best decided on the basis of the severity of the disease. Many cases such as those with cardiac failure or other serious complications should obviously be confined to bed. Others, and perhaps the majority, can be treated without restricting their daily activities. While it is helpful to be able to measure the basal oxygen consumption at frequent intervals, treatment can be carried out and the dosage regulated on the basis of clinical observations alone. The body weight, the basal pulse rate, and the appearance and behavior of the patient are helpful indices of the state of the metabolism. Often the patient himself becomes aware of the symptoms of an impending rise or fall in metabolic rate and can advise his physician accordingly.

The most prominent disadvantage of thiouracil is the occasional occurrence of toxic manifestations. It is suggested that the patient be made acquainted with the nature of the possible complications and impressed with the importance of giving prompt notice should malaise in any form be noticed.

If it be necessary to stop the drug a number of alternatives are at hand. Surgery can be safely carried out if the metabolic rate be normal. Iodine is effective and may be employed either during or after thiouracil therapy. It would be preferable to have at hand other

drugs of different chemical structure but with a comparable degree of antithyroid activity to be employed should sensitivity to thiouracil develop. Thiourea has been used for this purpose but as already pointed out it has the disadvantages of unpleasant taste and smell, low activity and a high incidence of attendant skin eruptions. More satisfactory compounds will be available for this purpose in the near future.

Dosage. In experimental animals it is possible to determine with precision the daily dosage required for a detectable effect upon the thyroid gland and the amount required to induce a complete or very nearly complete inhibition of thyroid hormone synthesis. In rats permitted to take thiouracil as a solution in the drinking water, a distinct fall in the iodine content of the thyroid gland follows in 10 days when as little as 0.3 mg. per 100 cc. is given in this way (9). This represents a daily dose of approximately 0.7 mg. per kilogram of body weight or about 50 mg. for a man of 70 kg. A full effect in the rat requires a concentration of 0.1 per cent in the drinking water, which is equivalent to a dose of 20 mg. per kilogram of body weight per day. This would correspond to a daily dose for a 70 kg. man of 1.4 gm. While such a comparison between the rat and man can at the best be an approximate one, the first estimates of clinical dosage were made in this way. In most of the early cases the initial dose was arbitrarily set at 0.6 gm. per day. This was exceeded in only one instance when 1 gm. daily was given for 28 days followed by 2 gm. daily for the next 8 days. This case, as previously reported (1), developed a severe but non-fatal agranulocytosis. While a daily dose of 0.6 gm. proved to be adequate initially, it soon became apparent that this had to be reduced when the metabolic rate reached normal in order to avoid abnormally low levels of metabolism.

As the desired clinical effect is one of partial rather than complete inhibition of the thyroid gland one might expect that the optimal dosage would correspond more closely with the minimal effective dose as determined in rats rather than with the dosage needed to induce cretinism or myxedema. Indeed the smaller doses which have been found to be effective clinically for example, 200 mg. per day, are only a little larger on a weight basis than the minimal effective dose in the experimental animal. One might reasonably expect that were the induction of fully developed myxedema in normal persons the aim of thiouracil administration, the larger doses, perhaps approaching 1 gm. per day, would be required.

It is clear, in experimental animals, that single large doses of thiouracil at infrequent intervals are less efficient in inhibiting the thyroid gland than are frequent small doses. This is what would be expected from the nature of the drug's action, and ideally one would aim to maintain a constant level of thiouracil in the body fluids. This would presumably require that doses be given at frequent intervals day and night—a procedure attended by obvious disadvantages. Six, eight, twelve and twenty-four hour intervals have been used in the cases reported here. There is evidence that one dose per day is less efficient than divided doses: for example, 0.1 gm. at twelve hour intervals maintained a lower metabolic rate than did 0.2 gm. once daily. The further subdivision of the daily dose into three or four doses at eight or six hour intervals did not result in any perceptible gain in effectiveness. Consequently the twelve hour interval has been adopted as a practical procedure; it has the further advantage that each dose can be taken on a full stomach immediately after eating, thus providing for a decreased rate of absorption from the intestinal tract.

Attempts to correlate the dosage needed in any individual case with either the severity of the disease or with the size of the thyroid gland were not successful. It should be pointed out, however, that the data are not sufficiently extensive to prove that the maintenance dose may not be slightly modified by these factors. Actually it is quite surprising how little individual cases deviate in their daily requirement from the usual maintenance dose of 0.2 gm. of thiouracil per day.

SUMMARY

A study of 62 cases is reported. The administration of 0.2 to 0.6 gm. of thiouracil daily in two doses quickly controlled all of the manifestations of hyperthyroidism in previously untreated cases of Graves' disease. The metabolic

response was slower in most cases of toxic nodular goiter, in iodine-treated Graves' disease and in normal persons. A temporary enlargement and increased vascularity of the thyroid gland was noted in some cases. Exophthalmos usually improved slowly. Iodine still exhibited its characteristic effect on patients with Graves' disease both during and after thiouracil therapy. Serious side-effects consisting of granulocytopenia and drug fever occurred in about 10 per cent of the cases during the early weeks of therapy. Adequate treatment, continued for longer than six months, was attended by a high incidence of lasting remissions.

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The Treatment of 26 Thyrotoxic Patients with Thiouracil and a Review of Toxic Reactions in All (135) Reported Cases

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IN THE two and one-half years since Mackenzie, Mackenzie, and McCollum (1) and Richter and Clisby (2) reported a striking goitrogenic action in animals as a result of the administration of sulfaguanidine and of phenyl-thiourea, respectively, no less than 51 articles have been devoted to a study of a number of aniline and thiourea derivatives of relatively low toxicity, which are capable of depressing the formation of thyroglobulin (3 to 53). A critically detailed analysis of the work covered by these communications is far outside the scope of the present report. However, several generally accepted facts emerge which may justify reiteration.

1. "Thyroid-active" sulfonamide and thiourea derivatives depress metabolism.

2. These compounds produce an enlargement and hyperplasia of the thyroid in animals and a hyperplasia in man.

3. The degree of hyperplasia may be quantitatively expressed through variations in the height of the follicular cell (20, 21, 37).

4. The hyperplasia appears to come about in the following way. Normally, thyroid hormone suppresses the thyrotropic activity of the anterior pituitary, thus establishing a balance between the two glands. The compounds mentioned decrease or stop the output of thyroid hormone, thereby partially or completely removing this inhibitory effect. Thus, the unchecked pituitary secretion produces a marked increase in the size of the thyroid cell. That this is true is suggested by the fact that either hypophysectomy or the feeding of thyroid hormone in sufficient doses abolishes the effect. Furthermore, the pituitaries of rats made goitrous by these drugs present the same histologic picture as do the pituitaries of thyroidectomized rats (6, 32, 33).

5. This hyperplasia, unlike that produced by Graves' disease or potassium thiocyanate, is not influenced by the administration of iodine.

6. However, definite alterations in iodine metabolism occur as a result of administration of certain aniline and thiourea derivatives. Iodine disappears almost completely from the thyroids of young rats treated with thiouracil or sulfadiazine (14, 15, 45) and from the thyroids of patients treated with thiouracil (44). Hypophysectomy decreases and thyroxin administration in sufficiently large doses inhibits this effect (8). In vitro, sulfanilamide did not interfere with the concentration of iodine by the thyroid, but prevented its conversion to di-iodotyrosine and thyroxin (46). Colloid formed under the influence of the two groups of compounds is, therefore, iodine-poor (24). Reaccumulation of iodine following release from the action of the drug is rapid, but may be considerably delayed by removal of the pituitary or the administration of thyroxin (8, 42). The point at which the formation of thyroglobulin is checked has not as yet been definitely determined, but the formation of di-

iodotyrosine and thyroxin have both been diminished (14, 15). This observation supports the suggestion of others that at least one action of thiouracil is "to interfere with the iodinization of the thyroglobulin molecule, thus preventing the elaboration of any physiologically active hormone" (45). In human subjects with thyrotoxicosis, it has been stated that previous or simultaneous treatment with iodine retards the action of thiouracil (7, 44); however, such an effect has also been denied (40).

7. Thiouracil retards the growth of young animals (26, 53). The impairment of growth involves the entire body exclusive of the thyroid. The pituitary, adrenals, and gonads of treated animals are smaller than those of siblings, but the decrease in the size of these glands is proportionate to the general decrease in body structure and weight.

8. Thiouracil furthers the adrenomegalic action of the adrenotropic hormone (53), hinders the stimulation of growth by the corresponding hormone, and augments the action of the thyrotropic hormone on the thyroid gland.

The discovery of the profound effect of thiouracil led to its almost immediate application to patients with thyrotoxicosis. Thus far, the reported number of patients treated has been comparatively small, totalling 109 (4, 7, 9, 11, 16, 35, 40, 44, 49, 51). In the majority of these reports, details of cases have been omitted. The final evaluation must come through the summation of the experiences of many observers. It is with that thought in mind that the present report has been prepared.

MATERIAL AND METHODS

Four male and 22 female patients with thyrotoxicosis have been studied while under treatment with thiouracil[1] (table 1). No change was made in the usual routine of living of twelve patients (*Cases #4, 5, 6, 7, 8, 9, 11, 12, 14, 15, 16,* and *17*). The remaining fourteen were hospitalized for longer or shorter periods, not because of the greater severity of the condition, as can be seen by reference to table 1, but with a view to more careful study and continuous observation. Patients were classified as "severely toxic" if the basal metabolic rate was plus 50 per cent or over; as "moderately toxic," if between plus 30 and plus 50 per cent; and "mildly toxic," if between plus 15 and plus 30 per cent.

In the hospitalized group, basal metabolic rates were taken shortly after admission to the hospital and again just before therapy was started, usually about one week later. The latter determination is recorded in table 1 as the "before" reading. During the first month of treatment, all patients were checked at least once weekly in regard to changes in subjective symptoms, pulse rate, blood pressure, weight, the blood count, and the basal metabolic rate; thereafter the blood counts and metabolic rates were determined every two weeks until a maintenance dose was well established. Finally these two tests were performed once monthly. In the hospitalized patients, subjective symptoms and physical findings were checked daily. In addition to the weekly determinations of the blood count and basal metabolic rate, the blood was examined at approximately weekly intervals for the levels of cholesterol and esters, phosphatase, proteins, sodium, potassium, and chloride. The icteric index, the cephalin flocculation, and Van den Bergh responses were simultaneously observed. Twenty-four-hour specimens of urine were anlayzed once weekly for the total amount of creatine and creatinine present. Laboratory procedures were those in general clinical use; slight variations in one or several of the blood chemical procedures have been described elsewhere (54).

In view of the rapid absorption and excretion of single doses of thiouracil, administration was so arranged as to distribute the absorption over the 24-hour period as evenly as possible. However, if four or fewer doses were required (0.1 gm. at each dose), this was given throughout the waking hours only. With 0.5 gm. and more, five doses were routinely used, beginning on awaking in the morning and at four-hour intervals thereafter until the fifth dose was taken. This regime avoided disturbing the patient in the early morning hours, and still allowed for reasonably uniform absorption.

[1] We are indebted to Dr. B. W. Carey, of the Lederle Laboratories, for supplies of thiouracil used in the pursuit of these studies.

TABLE 1. OBSERVATIONS IN 26 CASES OF THYROTOXICOSIS TREATED WITH THIOURACIL

Findings in relation to treatment

TABLE I. OBSERVATIONS IN 26 CASES OF THYROTOXICOSIS TREATED WITH THIOURACIL

Case #	Type goiter[1]	Age	Sex	Age at prev. op.	Findings in relation to treatment: Pulse Bef.	Pulse Aft.	Weight Bef.	Weight Aft.	Blood pressure Bef.	Blood pressure Aft.	B.M.R. Bef.	B.M.R. Aft.	Blood cholesterol Bef.	Blood cholesterol Aft.	Size of gland[2] Bef.	Size of gland[2] Aft.	Thiouracil: Dosage (gm.) Initial Daily	Initial Days	Maintenance	Approx. total	Duration of Rx: To normal B.M.R. (days)	Total (mos.)	Remarks[4]
1	H	65	F	57	96	64	114	125	160/70	164/100	+70	0	170	254	N	O	0.4	180	0.4	72.0	8	6.0	Fibrillation relieved. PA[3] years ago.
2	H	32	F	21, 29, 30	90	90	228	235	150/112	120/85	+22	+ 2	140	198	Sc	O	0.4	40	0.2	29.0	7	3.5	Markedly obese. Subjective symptoms relieved by thiouracil.
3	H	42	F	40	110	84	142	155	160/100	126/90	− 2	−15	88	219	L	D	0.4	28	0.2	47.7	—	6.5	BMR +34 on adm.; >to +2 in 6 wk. by rest, I_2.
4	MN	65	M	—	120	70	123	125	162/90	120/80	+53	−15	—	—	L	O	0.8	8	0.2	121.0	10	8.0	Myxed. developed on 0.3 gm. daily for about 5 mos.; B.M.R. <to +7 on 0.2. daily.
5	H	31	F	—	110	70	134	138	140/80	120/80	+15	− 1	140	180	L	D	0.5	9	0.3	30.6	9	3.5	Later B.M.R. +11.
8	MN	36	F	—	90	70	135	145	130/60	100/70	+51	+15	—	—	L	D	0.5	9	0.2	32.3	9	5.5	5 mos. pregnant when thiouracil started; normal delivery.
7	MN	55	F	32	112	72	111	130	210/85	130/78	+73	+ 9	165	205	L	O	0.5	25	0.3	46.1	60	4.0	
8	H	26	F	—	136	76	115	121½	160/78	114/78	+69	+ 3	—	—	L	D	0.8	19	0.3	57.4	18	5.0	Leukopenia, which disappeared without changing therapy.
9	N	48	F	—	112	80	112	123	150/72	110/78	+65	+ 8	—	—	L	O	1.0	5	0.4	96.0	5	7.5	Fibrillation relieved by thiouracil. Granulocytes dropped to 32% after 3½ mos. Rx. Return to normal while drug continued.
10	H	14	F	—	120	84	105½	112	106/60	112/68	+66	+24	130	170	L	D	0.5	5	0.2	35.6	—	6.0	Patient uncooperative.
11	H	53	F	—	120	80	136	150	160/60	118/80	+45	+ 9	230	—	Sm	—	0.5	5	0.2	40.8	12	7.0	Fibrillation relieved.
12	H	54	F	—	124	76	137½	142	204/68	208/86	+64	− 2	295	—	L	D	1.0	5	0.3	72.2	5	7.5	Diabetes not improved by thiouracil.
13	H	39	F	—	124	90	133	133	110/52	118/68	+40	+32	—	—	L	O	0.5	6	—	3.0	—	0.2	I_2 bef., with drug; Op. on 6th day of thiouracil.
14	H	44	M	29	88	88	178	180	130/70	126/74	+32	+11	—	—	N	O	0.3	12	0.3	24.2	26	3.0	Dose increased to 0.4 gm. on 14th day.
15	H	34	F	—	110	72	150	160	164/90	125/75	+24	+ 6	—	—	L	D	0.5	7	0.2	58.5	21	9.0	
16	H	38	M	—	120	80	135	140	160/80	120/78	+43	0	—	—	L	D	0.5	10	0.2	11.0	10	1.0	
17	H	50	F	—	108	72	102	111	140/90	124/80	+63	+ 1	220	280	L	D	0.5	42	—	21.0	14	1.75	Severe agranulocytic reaction. Table IV.
18	MN	64	F	23	100	80	106	110	206/82	120/60	+50	+12	182	230	L	D	0.4	62	0.3	24.8	59	2.5	Diabetic; insulin requirement increased under Rx from 40 to 50 U.PZI. Fibrillation relieved.
19	N	67	F	—	100	80	79½	94½	140/64	150/116	+57	+16	130	178	L	D	0.4	47	—	18.8	—	1.5	Diabetic. Hypertension for one year.
20	H	42	F	—	130	90	85½	94½	140/74	140/84	+53	+36	154	230	L	O	0.4	15	—	6.0	—	0.5	Mild diabetic. No insulin.
21	H	50	F	—	100	80	123	126	145.70	110/70	+58	+44	135	146	L	D	0.4	23	—	9.2	—	0.7	Fibrillation. WBC 4,600; 2,500; 6,500; polys. 46, 48, 56 before, 2nd, 3rd. weeks of treatment, respectively.
22	MN	46	M	—	120	72	120	117	135/70	126/66	+58	+34	161	152	L	D	1.0	14	—	14.0	—	0.5	Diabetic. Fibrillation.
23	H	38	F	—	100	88	148	148	160/60	130/90	+44	+24	132	176	L	I	1.0	14	—	17.5	—	0.7	
24	MN	35	F	32, 34	80	90	188	187	118/68	124/84	+53	+15	100	118	L	O	0.4	17	0.3	25.5	14	2.5	Fibrillation.
25	MN	59	F	58	80	80	124	126	88/65	100/60	+42	− 1	166	172	Sc	—	0.5	7	—	3.5	7	0.25	Severe febrile and urticarial reaction. Reproduced 10 days later by single dose 0.1 gm.
26	H	41	F	—	104	92	103	103	120/70	120/70	+26	+11	96	142	L	O	0.4	31	0.2	21.4	8	2.5	

[1] H = Toxic hyperplasia; N = Nodular; MN = Multiple nodular
[2] N = Normal; L = Large; Sc = Scarred and difficult to palpate; Sm = Small; O = No change; D = Decreased; I = Increased; — = Impossible to tell.
[3] PA = Pernicious anemia
[4] > = Decreased; < = Increased; ℞ = Treatment.

RESULTS

General data. Some of the facts from individual cases are summarized in table 1. Of the four male patients, three had a toxic hyperplasia, and one, a nodular goiter. Of the goiters in the 22 females, 15 were hyperplastic, and 7, nodular. The average age of the men was 48.3 years; of the women, 44.4. Eight of the patients had been previously operated upon, two on more than one occasion. Increased thyroid activity was recognized by the presence of some combination of a majority of the classical signs, with particular emphasis upon loss of weight, eye signs, tremors, hyper-reactivity, tachycardia, excessive perspiration, and an elevated basal metabolic rate. In evaluating the results of thiouracil therapy, particular attention was paid to the improvement in subjective symptoms, pulse rate, weight, blood pressure, blood cholesterol, basal metabolic rate, and alterations in the size of the thyroid gland. Patients have been followed under treatment for periods ranging from six days to nine months. In every instance, even when used for only six and seven days respectively (*Cases #13* and *25*), thiouracil brought about a recession of subjective symptoms. A decrease in the basal metabolic rate was observed in all but one patient; she had a normal rate when treatment was begun (*Case #3*). The influence of thiouracil was significantly exerted upon various functions noted below.

TABLE 2. TIME REQUIRED TO BRING ELEVATED BASAL METABOLIC RATES TO NORMAL WITH THIOURACIL IN VARYING DOSAGES

Pre-treatment B.M.R. (%)	Daily dose thiouracil (gm.)	# Patients	Normal B.M.R. after — days (Average)
+50 and over	0.4	3	27
	0.5	3	26
	0.8	2	14
	1.0	2	5
+30 to +50	0.4	2	10
	0.5	2	11
+15 to +30	0.4	1	7
	0.5	2	15

1. *Basal metabolic rate.* The average pre-treatment basal metabolic rate was plus 48 per cent, with the lowest, minus 2 per cent, and the highest, plus 73 per cent. After treatment the average rate was plus 9.2 per cent, with the lowest minus 15 per cent, and the highest, plus 44 per cent. The latter figure was seen in a patient (*Case #21*) whose initial dose of thiouracil was low (0.4 gm. daily) and duration of treatment, three weeks. She improved subjectively, with a lowered pulse rate, an increased or stationary weight, an increased cholesterol, and a decreased pulse pressure. The basal metabolic rate was considered normal if plus 15 or below. Under treatment, "normal" values were observed in 19 patients, in one of whom (*Case #3*) the figure was normal before therapy was instituted. In the remaining 18, it took an average of 16 days to bring the metabolism to normal with the dosages used. Sixty days were required in one patient with a toxic multiple nodular goiter who was given an initial dose of 0.5 gm. daily. In two patients the rate was reduced to normal within five days of treatment; each of these was severely toxic. One (*Case #9*) had an adenoma, and the other (*Case #12*) showed a diffuse swelling of the gland; both received 1.0 gm. of thiouracil daily. The second of these patients had a co-associated diabetes mellitus. Sugar tolerance has not been materially affected by the successful control of her hyperthyroidism for a period of approximately seven and a half months.

Some direct relationship appears to exist between the dosage of thiouracil employed, the degree of elevation initially observed in the basal metabolism, and the number of days necessary to establish a normal level for it (table 2). In so small a series, the actual figures are not statistically significant but they suggest the quantitative nature of the action of thiouracil. The effect of the drug in lowering metabolism is as easily produced in the patients with nodular goiter as in those with a toxic hyperplasia.

2. *The pulse rate.* The average pre-treatment pulse rate in the 26 patients was 109 per minute, and after therapy, 79 per minute. The pulse rate was not appreciably affected in four of the patients (*Cases #2, 14, 24,* and *25*) who showed a good response to the medication. However, in each of these it had initially been 90 or below when the patient was first observed.

3. *The blood pressure.* If we accept 150 mm. of mercury as the upper limit of normal for the systolic blood pressure, then a high figure was seen in 11 of the 26 individuals, in two of whom (*Cases #1* and *#12*) there was a previous history of benign hypertension. Following treatment with thiouracil the systolic blood pressure was well within the normal range except for the two patients with known hypertensive disease.

If "cardiac load" is measured in terms of the ratio between pulse and diastolic pressures and a figure of 0.5 is considered the upper normal limit, then 24 patients had abnormally high ratios, and in 14 of these it exceeded 1.00. After treatment nine patients had ratios of 0.5 or below, while the ratio remained above 1.00 in one case of hypertension only. This change in cardiac load was often one of the earliest favorable signs of decreasing toxicity.

4. *Weight.* Restrictive diets were used in two patients (*Cases #2* and *#24*) who were obese at the onset of treatment; despite that, one of these gained several pounds. If no effort was made to control the weight, there was invariably an increase in those patients who were carried to complete control of their thyrotoxic condition. With the exception of those who were obese, patients were allowed to follow the dictates of appetite. Moreover, in those who were ambulatory, no attempt was made to enforce rest periods which might have aided in the conservation of body energy.

5. *Blood cholesterol.* The ratio of esters to total cholesterol was not significantly disturbed in any of the 18 patients in whom determinations were made. In our laboratory, total cholesterol values ranging from 150 to 200 mg. per 100 cc. are accepted as normal. Low values were initially observed in three instances, but one of these was obtained in a severely toxic patient. Initially high values were noted in three individuals, one of whom (*Case #12*) was a diabetic not fully controlled at the time of the determination. The second (*Case #11*) was moderately toxic, while the third (*Case #17*) was severely so. Little importance can be attached to the initial values for total cholesterol, but their tendency to rise under treatment and to fluctuate inversely as the basal metabolic rate was rather striking. Serial determinations were carried out in 16 patients. In but one (*Case #22*) were the values lower at the end of the period than they had been initially. In this instance the basal metabolic rate dropped from plus 58 to plus 34 per cent in 14 days, while the cholesterol decreased from 161 to 152 mg. per 100 cc. It must be emphasized that absolute values for cholesterol were of relatively little importance, while increases from the initial level almost always accompanied clinical improvement and a falling basal metabolic rate. Furthermore, a decrease in blood cholesterol was invariably observed during exacerbation of the thyrotoxic state whenever the drug was stopped.

6. *Size of the thyroid gland.* One patient had a small gland and two, a normal sized gland at the beginning of treatment. In two there was so much scarring from previous operative procedure that no conclusion as to the size of the gland could be reached. Of the remaining 21 patients with definitely enlarged glands, seven showed no appreciable change in size under treatment. In 13 the decrease in size was readily apparent, and in one an actual increase occurred, later followed by a decrease. In the last mentioned, the increase was most marked between 11 and 14 days, while her basal metabolic rate was at the pre-treatment level (plus 44 per cent), although some symptomatic improvement had occurred. At 21 days the decrease from the initial size was definite, and the basal metabolic rate was plus 24 per cent. Of the 14 patients in whom a decrease in size was noted, nine had a toxic hyperplasia, and five, a nodular goiter.

The maintenance dose of thiouracil. After the basal metabolic rate of thyrotoxic patients has been reduced through thiouracil administration to normal, the continuation of therapy is essential to prevent its rise with the concomitant recurrence of other toxic manifestations. The dosage of drug necessary to keep the rate reduced to within normal limits may be defined as the "maintenance dose." In 18 patients this has varied from 0.2 to 0.4 gm. daily, given in divided doses of 0.1 gm. each. Table 3 shows the maintenance dose in relation to the initial basal metabolic rate. One of the more severely thyrotoxic patients (*Case #4*) was maintained for approximately four months on 0.3 gm. daily. He then developed a frank

myxedematous state with a basal metabolic rate of minus 15 per cent; difficulty in concentrating; hoarseness; sleeplessness; puffiness; thickening and dryness of the skin; slowness in action, thought, and speech; and a pulse rate of 70. These began to abate four days after stopping the drug. At first, his ability to sleep improved, then his capacity for concentrating at work increased, and finally the changes in the voice and skin disappeared. At the end of seven days his basal metabolic rate was plus 3 per cent. For the three months since the myxedema occurred, he has been satisfactorily controlled by the use of 0.2 gm. of drug daily, with his basal metabolic rate ranging between plus 3 and plus 10 per cent.

TABLE 3. DAILY MAINTENANCE DOSE OF THIOURACIL IN RELATION TO THE PRE-TREATMENT BASAL METABOLIC RATE

Initial B.M.R. (% of normal)	No. of Patients	Daily dose of thiouracil (gm.)
+50 and over	2	0.4
	5	0.3
	3	0.2
+30 and +50	1	0.3
	2	0.2
Up to +30	1	0.3
	4	0.2

Attempt has been made to maintain a normal functional status of the thyroid in several patients with doses of 0.1 gm. daily, but so far every patient so treated has showed evidence of recurring toxicity. For each patient whose control or maintenance dose is mentioned in table 3, unsuccessful effort was made to decrease the dose by 0.1 gm., provided the basal metabolic rate had been found between 0 and plus 10 per cent in three successive tests. Therefore, the "maintenance dose" in each instance has been arrived at by rather careful "trial and error" methods.

Other studies. In nine patients several additional procedures were carried out with a view to ascertaining the further metabolic effects of thiouracil. Blood sodium, potassium, and chloride levels were unaffected by the drug. Hippuric acid excretion was normal before and after treatment. No appreciable change occurred in the glucose tolerance of any patient. The initial curves were within normal limits except in the patients with frank diabetes and in these the test was not always done. Four patients had diabetes; the insulin requirement was altered in one (*Case #18*), who after treatment with thiouracil required more insulin than formerly (table 1). No evidence of liver damage could be found in any of our patients by the use of hippuric acid excretion tests, glucose tolerance curves, determination of icteric indices, cephalin flocculations, and van den Bergh reactions. No constant effect was observed on blood proteins and at no time were the values for them frankly abnormal. Blood phosphatase figures were normal. Despite the fact that no attempt was made to keep our patients at any time on a creatine-free diet, the amount found in the urine increased with mounting toxicity and decreased when the patients were fully controlled. Complete blood counts made on all patients at frequent intervals as previously mentioned showed initially, in the majority of cases, the lymphocytosis accepted as characteristic of thyrotoxicosis, the lymphocytes ranging from 35 to 65 per cent in the "pre-treatment" studies. There was a tendency for intensification of the lymphocytosis, usually between the second and third weeks of treatment, or more accurately, about the time the basal metabolic rate first approached normal, following which a normal differential count was usually obtained.

In the pre-treatment period, seven of the 26 patients showed paroxysmal attacks of fibrillation. Without digitalis therapy, this disappeared in each instance as soon as the basal metabolic rate fell to within normal limits. The most dramatic change was noted in a patient (*Case #9*) with an initial pulse rate of 140. No attacks of fibrillation were observed five days after the drug was begun, at which time her former basal metabolic rate of plus 65 per cent had decreased to plus 8.

Toxic reactions. None of our patients showed any nausea or gastric distress during or following the administration of thiouracil. Three patients (*Cases #8, 9,* and *21*) developed leukopenia with intensification of the lymphocytosis already present. In these, the white counts were 3,500, 4,500, and 2,500, respectively; and the percentage of polymorphonuclear leucocytes was 41, 32, and 48, respectively. When

the "reactions" occurred, the first and second of these patients had been under treatment on maintenance doses of 0.3 and 0.4 gm. daily for two and a half and five months, respectively. In the third patient the altered count was noted after 0.4 gm. of the drug had been administered daily for one week. Without changing the treatment in any of these three patients, the blood counts of each reverted completely to normal. It is questionable, therefore, whether we should look upon these responses as pathological or physiological. However, there was one patient (*Case #17*) in whom the nature and severity of the lesions leave little doubt as to their toxic character, and a second (*Case #25*) in whom the abnormal response must be attributed to hypersensitivity (table 4). The findings in these will be summarized here and described in detail elsewhere (55).

TABLE 4. FINDINGS IN 2 PATIENTS WITH AN UNTOWARD REACTION TO THIOURACIL

Patient	Day of reaction[1]	Thiouracil (gm.)		Blood count								Nature of reaction and comments
		Daily dose[2]	Total dose[2]	Hgb. (%)	RBC mill./ cu. mm.	WBC thous./ cu. mm.	Differential white count (%)					
							P	L	M	E	B	
#17	7B	0.5	17.5	84	4.30	7.90	57	38	3	1	1	Agranulocytic angina
	2	—	21.0			3.50	0	97	1	1	1	
	3			80		2.24	0	98	2	0	0	
	5					1.40	0	98	2	0	0	
	6					1.70	1	96	3	0	0	Temp. normal
	8					3.60	11	83	4	1	0	
	13			85	4.50	7.65	67	26	5	1	1	Patient fully recovered
#25	9B	0.0	0.0	79	3.85	12.20	83	14	1	2	0	Urticaria; fever
	1	0.5	3.5			9.00	84	10	3	0	0	Metamyelocytes, 1%; myelocytes, 2%
	2			80	4.75	8.80	70	28	0	0	2	
	3					9.10	40	48	2	0	0	Temp. 104°F.
	4					9.60	42	54	2	2	0	Temp. normal
	5			80	4.70	11.35	75	23	0	2	0	
	6			68	3.50	12.80	79	18	2	0	1	
	11			78	4.00	14.10	85	7	3	0	0	Meylocytes 5%

[1] B = Before reaction
[2] At or to the time of the reaction

The first of these reactions occurred in a 50-year-old, white woman with the classical signs of a toxic hyperplasia of the thyroid and an initial basal metabolic rate of plus 63 per cent. This was reduced to plus 21 per cent in 14 days, and to plus 3 per cent at the end of 21 days. Despite this, through a misunderstanding her physician continued the dose of 0.5 gm. daily. At the end of the fifth week her blood count was still normal. On the forty-first day of treatment she slept poorly, developed a slight temperature, and the next day had a sore throat, gingivitis, headache, and sore cervical glands. A blood count taken at this time showed 3,500 white cells with 97 per cent lymphocytes. Thiouracil was stopped, and several transfusions were given. A bone marrow study revealed a decrease in the myeloid series of cells and an increase in the lymphocytes, hematogones, and reticulum cells. A differential count of bone marrow cells was as follows: myeloblasts, 2.0; neutrophilic myelocytes, 41.2; eosinophilic myelocytes, 0.4; metamyelocytes, 17.2; lymphocytes, 17.2; hematogones, 7.8; plasmatocytes, 0.8; erythroblasts, 0.08; and normoblasts, 18.0. On admission to the hospital, her clotting time was 10 minutes; her Rumpel-Leede test, positive; the icteric index, 6; and total blood proteins, 6.6 gm. per 100 cc. Her blood culture was negative. Her temperature was 102° F. on admission and gradually fell to normal in 6 days. At the time of discharge, the blood and bone marrow counts were normal. In retrospect it would appear that stopping the drug without any recourse to transfusion would have adequately relieved her condition, particularly in view of the fact that less severe lymphocytic and leukopenic reactions disappeared spontaneously in other

patients while treatment was continued. In this instance, the continued large dose of the drug was undoubtedly responsible for the reaction. It was much greater than that necessary to maintain the patient in a symptom-free state with a normal basal metabolic rate.

The second patient (*Case #25*) who had an untoward reaction was a 59-year-old white woman. She had been operated upon one year previously for a "toxic goiter" and entered the hospital for treatment of recurrent thyrotoxic symptoms and hypoparathyroidism. Her basal metabolic rate was plus 42 per cent. On the seventh day after receiving 0.5 gm. thiouracil daily, she developed a temperature of 102.6° F., an urticarial rash over both forearms and legs, and a leukopenia with lymphocytosis. The temperature subsided in four days; the rash, in ten; and the blood count reverted to normal during that interval. Ten days after the reaction subsided, a single dose of the drug was inadvertently given, with the reappearance of all the previously noted symptoms and findings. However, this second reaction was less severe and lasted only three days.

DISCUSSION

1. *Toxic reactions.* For a long time the treatment of thyrotoxicosis has baffled the combined skill of surgeon and internist, neither of whom has made any very fundamental contribution to its therapy since the recognition of the role probably played by iodine. Therefore, it is natural that any drug which is capable of acting more or less specifically on the thyroid to depress the formation of thyroglobulin should be received with the greatest enthusiasm. In the case of thiouracil we have such a drug; its extended use will depend chiefly upon whether its beneficial effects can be obtained without incurring undue risk as a result of its toxic action. A careful evaluation of this point is primary to any consideration of the problem as a whole. Fruitful discussion must of necessity involve a review of all reported cases, with particular reference to untoward reactions. A summary of pertinent data is contained in table 5, in which 109 cases previously reported and the present series of 26 cases are reviewed in relation to toxic reactions. In addition, seven patients have undergone treatment with thiourea. Sixteen of the 135 patients treated with thiouracil and one of the seven given thiourea developed toxic reactions. The majority of these have involved the hematopoietic system.

The picture of *agranulocytic angina* was produced in two patients receiving thiouracil (4, 7) (*Case #17*) and in one taking thiourea (38). In the last mentioned, a widespread purpuric eruption was also present. The patient had received a total of 83 gm. of thiourea distributed over a five-week period of observation. Thiouracil had been given to one of the other patients (4, 7) in doses of 2.0 gm. daily for six days following the use of 1.0 gm. daily for 27 days. No granulocytes were present in blood smears and the total white count was reduced to 1,000 per cu. mm. Our patient, *Case #17*, had received 0.5 gm. daily for six weeks before a reaction occurred similar in kind and degree to that just described (table 4). Despite the alarming symptoms presented by each of these patients, their recovery appeared to be complete and was not followed by any detectable disturbance in bone marrow activity or in general health.

Leukopenia and *relative lymphocytosis* have been noted in three of our own patients and mentioned as unfavorable responses by at least two other observers (16, 40), involving three patients. In our patients the reaction subsided without interrupting the treatment. It seems important to emphasize the dosages we were using at the time of the altered hemogram. In two instances the amount was 0.4 gm. daily, and in the third, 0.3 gm. daily. In the three cases reported by others, the drug was stopped with a prompt reversion of the hemogram to normal. In view of the relatively large maintenance doses we were using and the asymptomatic course of the hematopoietic response with spontaneous reversion to normal, it seems difficult to be sure that moderate leukopenia with lymphocytosis can be considered as a toxic phenomenon. In any event, it hardly warrants complete cessation of therapy. A middle and perhaps more satisfactory course would be to consider such responses an indication for temporary or permanent decrease in the size of the dose employed.

Fever was the chief toxic manifestation in

four patients taking thiouracil (7, 16) (*Case #25*) and has occurred in several others (4, 7) (*Case #17*). In Gabrilove's patients (16), it appeared after taking 1.0 gm. of thiouracil for eight and ten days respectively. Astwood's patient (7) had received 0.6 gm. daily, and ours had had 0.5 gm. daily for seven days. The common association of urticarial skin rashes, the fluctuant nature of the fever, and the smallness of the total dose received lead to the conclusion that such reactions are probably more in the nature of a true sensitivity than the end result of a cumulative toxic reaction. This point seems to have been confirmed in our case, in whom the entire reaction was reproduced by a single dose of the drug given later.

Diarrhea has been reported as the only toxic manifestation in one patient (7).

Williams and Bissell (51) saw mild reactions in three of nine patients treated. In two of these, slight pitting *edema* with elevation of serum chloride and decrease in carbon dioxide combining power occurred. In a third patient, they noted swelling and tenderness of the submaxillary glands. In all three patients the reactions disappeared without discontinuing therapy which consisted of 1.2 gm. thiouracil daily.

TABLE 5. INCIDENCE OF TOXIC REACTIONS IN ALL REPORTED CASES OF THYROTOXICOSIS (135) TREATED WITH THIOURACIL

Author	# cases reported		Dose of drug (gm.)[1]		Nature of reaction[2]	Drug (gm.)[3]	Remarks
	Total	Toxic reaction	Initial	Maintenance			
Astwood (4) (7)	30	4	0.3–0.6	0.1–0.3	Agranulocytosis—1 Fever—2 Diarrhea—1	2.0 0.6 0.6	Agranulocytosis represented the only severe reaction.
Williams, Bissell (51)	9	3	1.0	0.2–0.4	Edema—3 Enlarged glands—1	1.2 1.2	Reactions were all mild and disappeared without changing therapy.
Palmer (40)	12	2	0.8	0.4	Edema—2 Hematuria (microscopic)—1	1.0 0.4 to 1.0	Two patients had transient leukopenia with normal differential. Edema in one subsided without change in treatment.
Gabrilove (16)	9	3	1.0	1.0?	Leukopenia—1 Fever—2	1.0 1.0	At 16th day. At 8th and 10th days, respectively. One had urticaria; the other, large glands.
Bartels (9)	11	0	0.6	0.6			
Mayer (35)	5	1	0.5–0.8	0.4	Urticaria—1	0.8	Disappeared without stopping drug.
Dore (11)	4	0	0.6				
Sloan, Shorr (49)	4	1	0.8	0.8	Jaundice—1	0.8	No demonstrable hepatic damage. Two other patients mentioned who had rash only.
Rawson et al. (44)	25	0	0.6	0.4–0.6			Medication used preoperatively in 19.
McGavack et al.	26	2	0.4–1.0	0.2–0.4	Agranulocytosis—1 Fever, urticaria—1	0.5	Total dose 21.0 gm.
TOTAL	135	16					

[1] Represents the average daily dose used throughout the author's series of cases—not necessarily the dosage on which reaction occurred. See footnote 3.
[2] Figure to the right represents number of patients affected.
[3] Actual dosage in use at time of reaction.

Urticarial rashes, usually associated with fever, and a depression of the leucocyte count have been a prominent feature of five cases (16, 35, 49) (*Case #25*). In the first mentioned and the last three of these, the drug was stopped. In the second, the rash appeared after more than 35 days of treatment with 0.4 gm. thiouracil daily and disappeared without the interruption of therapy. In one of these patients (49), no details are given. As aforesaid, it is difficult to decide whether skin rashes arise as a result of hypersensitivity or toxicity. One would be inclined to look upon the response as hypersensitivity in three of the above patients (16) (*Case #25*) and in one of these this seems to have been proved (*Case #25*). In Mayer's patient (35) a toxic effect might be expected, although the dose of drug used was not excessive. In the fifth patient no accompanying data are given from which any conclusion might be drawn.

Mild *jaundice* with an icteric index of 23 has been described following 20 days of thiouracil, 0.8 gm. daily (49). The reaction subsided completely within ten days after the drug was stopped and no temporary or chronic interference with liver function could be detected in any of several tests.

The *hematuria* observed in one patient was microscopic in degree (40) but emphasizes the close relationship existing between the behavior of thiourea derivatives and the sulfonamides. However, since blood concentration is a major factor in the production of renal calculus by both groups of drugs, even the highest recommended doses of thiouracil should seldom cause renal complication.

From the above, it appears that *some form of toxic reaction* has been observed in 16, or 11.8 per cent, of 135 patients who have received thiouracil for the treatment of thyrotoxicosis. No fatal complications have been observed, but two of the patients were severely ill (4 7) (*Case #17*). Eight of the 17 reactions reported were very mild and seven of these eight were not considered sufficiently severe to justify the interruption of treatment. Before final judgment may be expressed the appearance of reactions in relation to daily and total doses should be carefully considered and weighed. One patient's reaction (35) occurred after the daily ingestion of 0.4 gm. of thiouracil and a total dose of 14 gm. Three patients had 0.6 gm. of the drug daily (7); another, 0.5 gm. daily for seven days (*Case #25*); and finally, one received 0.5 gm. daily for six weeks (*Case #17*). All of the other reactions were the result of much larger daily doses—from 0.8 to 2.0 gm. Two of the reactions from the smaller daily doses were so mild that therapy was not discontinued, while two of the other reactions at lower dosage levels were severe. One of these was an instance of hypersensitivity; we believe the other resulted from failure to heed the warning signs of an impending argranulocytosis. Astwood's contention (4) that reactions will rarely be seen if large doses are avoided, particularly for any length of time, seems to be well borne out by the experience of all observers. It might be well to add that where initially large doses seem advisable, complication is not likely to occur if the amount of the drug used daily is systematically reduced after a preliminary period not exceeding seven days' duration.

2. *The size of the thyroid gland.* Transient increases in the size of the gland have been noted (40, 51), followed by a decrease (51) (*Case #23*). In the majority of reports, no mention is made of variations in the size of the human thyroid under treatment. In animals, the early enlargement is followed much later by involution. While we were on the lookout for swelling of the gland early in our patients, we have thus far found an appreciable difference in but one patient, who, after a very short time, showed a diminution (*Case #23*). A decrease in the size of the tumefaction has been the rule. This has occurred not only in the toxic hyperplasias but with approximately equal frequency in the "adenomatous" lesions.

3. *The basal metabolic rate.* That the influence of thiouracil on the basal metabolic rate is due to a specific inhibition of the formation of thyroglobulin needs no further emphasis. It is interesting to note, however, that the elevations in rate seen in cardiac patients and in cases of arthritis and diabetes mellitus are not influenced by its action, at least when given for a relatively short period of time (4).

In thyrotoxicosis a quantitative relationship seems to exist between the rapidity of the action of thiouracil and the pre-treatment meta-

bolic rate. In the more toxic patients, it would appear to be desirable to lower the basal metabolic rate as rapidly as possible, particularly if they are to remain ambulatory. Therefore, in these, the larger doses (0.8 to 1.0 gm.) should be employed for short periods of time (five to ten days) without hesitancy, but should not be continued indefinitely, even though the metabolism has not been strikingly reduced at end of five to ten days. Early, i.e., in the first several weeks, the "maintenance dose" of the individual seems to bear some rather direct relationship to the initial toxicity, although one would hardly want to hazard a rule concerning this at the present time. Later, after a number of weeks of treatment, it seems likely that all patients will require approximately the same amount of drug. Our patient *#4* is a case in point. For approximately five months he required a maintenance dose of 0.3 gm. of drug daily, at the end of which time he developed the full-fledged picture of myxedema. The symptoms of myxedema disappeared after the drug was stopped for one week. Since then, a dose of 0.2 gm. daily has created and maintained a satisfactory thyroid status. In the main, our maintenance dosages for the more severe cases have been slightly larger than those deemed adequate by Astwood (4, 7). Although we have tried on a number of occasions to reduce some of the initially more toxic patients to doses of 0.2 gm. daily, with the exception of the one just mentioned, they have responded by slowly rising basal metabolic rate, sometimes associated with early mild toxic symptoms.

4. *Carbohydrate tolerance.* We were unable to detect an expected improvement in carbohydrate tolerance in any one of our four diabetics and in one the tolerance decreased without demonstrable cause. The early high peak in the curve ordinarily seen in thyrotoxic patients without diabetes disappeared under treatment. Astwood (4) described a diabetic with thyrotoxicosis who, under treatment with thiourea, was able to discontinue the daily use of 40 units of protamine zinc insulin. This is the type of reaction one would expect from thiourea or any of its "thyroid active" derivatives. However, Williams and his associates (52) have found no alteration in the gluconeogenic activity of the adrenals following the use of thiouracil in normal subjects or in patients with hyperadrenocorticism.

5. *Auricular fibrillation.* Whether or not fibrillation in thyrotoxicosis is a specific functional disturbance or merely an expression of added cardiac load is still unsettled. In any event, thiouracil rather dramatically caused its disappearance in seven patients.

6. *Influence of thiouracil on cholesterol, creatine, and other metabolites.* The rise in blood cholesterol values as a result of the administration of thiouracil is a logical result of the reduction in available thyroid hormone. However, similar variations have been seen in hypertention from doses of the drug which have not in any material way affected the basal metabolic rate (56).

The creatinuria of thyrotoxicosis is reduced by thiouracil (49, 52), and the retention of nitrogen, phosphorus, calcium, sodium, and chloride is favored (49, 52). The change in creatinuria is so striking that a creatine-free diet was not necessary for its demonstration in our patients.

7. *Recommended scale of dosage for the administration of thiouracil.* It is naturally desirable to obtain the maximum effectiveness of thiouracil and a minimal danger from the as-yet all-too-frequent toxic reactions. From careful scrutiny of the present group of cases, it would seem justifiable, therefore, to adjust our initial dosages in relation to the pre-treatment basal metabolic rate. For rates above plus 50 per cent, 0.8 to 1.0 gm. of the drug should be used over periods of from five to ten days, rarely longer. In the moderately severe case with a metabolism between plus 30 and plus 50 per cent, 0.6 gm. should be the initial dose, and in cases with a basal metabolic rate below plus 30 per cent, 0.4 gm. daily will be sufficient as a rule. In all cases the final "maintenance dose" will be an individual matter, but it is desirable to utilize 0.2 gm. or less daily whenever possible.

8. *General position of thiouracil in the therapy of thyrotoxicosis.* The strikingly specific action of thiouracil on the production of thyroid hormone may have given rise to the hope that surgery, which is not a fundamental cure for thyrotoxicosis, might in this regard be relegated to

the limbo of useless procedures. Such a course is probably not possible and certainly not desirable. In the light of our present knowledge, it would seem justifiable to use thiouracil instead of iodine in the preparation of all thyrotoxic patients on whom surgery is contemplated. Results of therapy with thiouracil have been sufficiently promising to warrant its extended and prolonged use in cases of toxic hyperplasia with a view to avoiding operative procedure. However, in this connection the toxic action must ever be kept in mind, and the clinician must be prepared to change his course when faced with early signs of unfavorable reaction.

So-called adenomas of the thyroid as a rule warrant surgery whether they are toxic or nontoxic. Formerly, their toxicity was feared, as it did not respond satisfactorily to iodine. Thiouracil acts as readily in adenomas as it does in the diffusely hyperplastic gland. Despite this fact, these tumefactions still remain as a possible mechanical problem and as the precursor of a cancerous lesion, which develops in about 3.7 per cent of all nodular goiters. Therefore, it seems wise to use thiouracil at least for the present to prepare patients with nodular goiter for surgical procedure.

SUMMARY

The course of 26 thyrotoxic patients under treatment with thiouracil has been followed for periods ranging from six days to nine months. Particular attention has been paid to variations in subjective symptoms, pulse rate, blood pressure, weight, basal metabolic rate, and blood cholesterol. These have been brought into relationship with the severity of the original toxic state and the dosage of the drug.

Characteristic effects in the adequately-treated patient included a lowering of the basal metabolic rate, a decrease in pulse rate, a narrowing of the pulse pressure with diminution in the systolic figure, an increase in weight, and an elevation of the value for total blood cholesterol.

The size of the thyroid was moderately decreased under treatment with thiouracil, and creatinuria was diminished.

No variations in blood cholorides, sodium, or potassium were observed. Tests of liver function failed to show abnormality before or during treatment.

Two of the 26 patients had severe toxic reactions. One developed agranulocytosis; the other, a fever and widespread urticarial rash.

Mention is made of all reported cases to date treated with thiouracil, 109 in number exclusive of the 26 cases herein reported.

In the total of 135 cases studied to date, there were 16 (11.5 per cent) that exhibited a toxic or hypersensitivity reaction. These cases are reviewed in detail.

In an effort to minimize unfavorable responses, the pre-treatment basal metabolic rate and clinical picture have been made the basis for suggesting rules of dosage for the administration of thiouracil.

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A Human Pregnancy Test Based Upon a Color Reaction of Pregnandiol in the Urine[1,2]

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IN THE NORMAL human menstrual cycle, pregnandiol is found in the urine from the ninth day until one to four days prior to the onset of bleeding (1–3). The consistency of this finding, in spite of a variable quantitative excretion in any one cycle, has led to an association between pregnandiol and corpus luteum activity.

If fertilization occurs and normal pregnancy ensues, then pregnandiol excretion continues at or above the maximum level reached during the latter half of the menstrual cycle. The excretion increases rapidly between the 60th and 90th day of pregnancy, reaches a peak shortly before parturition, and stops 24 to 48 hours after delivery (4–7). Despite quantitative variation in individual cases, this general pattern of pregnandiol excretion persists.

In the first two months of pregnancy, progesterone, secreted by the corpus luteum, is probably the chief source of pregnandiol in the urine. The spurt in pregnandiol excretion in the third month, with simultaneous regression of the corpus luteum, is probably due to placental secretion of progesterone or another pregnandiol precursor (8). Desoxycorticosterone as well as progesterone give rise to pregnandiol (9–12). Therefore, with the exception of adrenal cortical hypertrophy or tumors (13), pregnandiol in the urine is derived from progesterone secreted by the corpus luteum or by the placenta.

The possibility of utilizing the presistence of pregnandiol excretion after fertilization as an aid in the diagnosis of pregnancy has been previously suggested (14–16). However, the methods usually employed for urine pregnandiol determinations are time-consuming, expensive, and require expert technical help (17–22).

The qualitative color test for pregnandiol here presented employs simple procedures and requires only three hours to complete. A morning urine sample of 100 cc. is used, and the "positive" color obtained is orange to orange-brown, which indicates that 1 mg. or more of pregnandiol is present in 100 cc. of urine. In our experience, such a positive reaction in a patient with amenorrhea indicates a normal pregnancy.

The color obtained in this test seems to be specific for pregnandiol in view of the following considerations.

1) Absorption curves (using a Cenco spectrophotelometer) on the colored compound obtained from pregnancy urine show a maximum band at 430 mμ, identical with the band shown by pregnandiol and sodium pregnandiol glucuronidate added to male urine and subjected to the same procedure. The addition of estriol, estradiol, cholesterol or androsterone to urine and repetition of the procedure does not lead to the formation of complexes with this band of absorption.

2) The precipitate obtained in the test which is responsible for the color reaction has a melting point which is consistent with that of pure

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pregnandiol. When the precipitate is mixed with pure pregnandiol, the melting point of the latter is not depressed.

METHOD

First morning urine specimens of patients who presented the symptom of amenorrhea and constituted problems in diagnosis of pregnancy were used for the procedure. Tests were performed simultaneously by the color and Friedman methods. In abnormal pregnancies several urine specimens were examined until the course of the pregnancy was considered established. The clinical course of the patients was followed up to check the accuracy of the tests.

The method consists essentially of the extraction with toluene of the acid-hydrolyzed pregnandiol complex of urine, followed by the purification and precipitation of the pregnandiol. The characteristic color is developed by H_2SO_4. It has been our experience that four to six tests can be run simultaneously by one person in three hours. The technical details of the method follow.

TECHNIQUE[4]

A. *Hydrolysis and Extraction of Pregnandiol.*

1. One hundred cc. urine (first morning specimen), 50 cc. toluene (C.P.), 10 cc. conc. hydrochloric acid, and 2 glass beads are added to a 500 cc. flat-bottomed Florence flask.
2. The flask is connected via a one-holed cork stopper to a vertical Liebig condenser (water-cooled, 400–500 cm. jacket length) and the mixture is boiled vigorously over an electric hot-plate for 15 minutes.
3. The flask and its contents are brought to room temperature by cooling under the water tap.
4. The mixture is transferred to a 500 cc. separatory funnel, and the lower layer (urine) is drawn off.
5. The toluene layer and the toluene-water emulsion are washed twice with 15 cc. portions of 0.1 N sodium hydroxide and then twice with 15 cc. portions of distilled water.

B. *Precipitation of Impurities.*

1. The washed toluene and toluene-water emulsion (A-5) are transferred to a 125 cc. Erlenmeyer flask with 2 glass beads.
2. The mixture is boiled over an electric hot plate (in the hood).
3. When the water has evaporated and the toluene mixture is boiling smoothly, 10 cc. of 2% sodium hydroxide in absolute methanol is added.
4. The mixture is evaporated until one-half of the original toluene volume is reached.
5. The toluene mixture is then filtered, while hot, through a fritted glass filter (medium porosity, Pyrex) with mild suction. (If the filtrate has an orange, pink or brown tinge, steps B-3, B-4, B-5 must be repeated until the filtrate is yellow or yellow green.)
6. The precipitate (B-5) is washed with 15 cc. hot toluene.
7. The combined filtrates (B-5 and B-6) are then evaporated to dryness over the hot plate (in the hood), a gentle air stream being used to drive off the last traces of toluene. This avoids charring of the residue.

C. *Precipitation of Pregnandiol.*

1. Five cc. acetone is added to the residue (B-7) and the mixture is warmed over a hot plate until the solution is complete.
2. Twenty cc. 0.1 N sodium hydroxide is added slowly while the mixture is still on the hot plate.
3. The flask is then placed in an ice-water bath for 30 minutes or in a refrigerator (5°C.) for one hour.

D. *Isolation of Pregnandiol.*

1. The mixture (C-3) is filtered through a fritted glass filter (medium porosity, Pyrex) with mild suction.
2. The precipitate (D-1) is washed with 15 cc. distilled water.
3. The receiving flask is changed, and 10 cc. hot absolute alcohol is passed through the fritted glass filter to dissolve the precipitate.
4. The alcohol filtrate (D-3) is evaporated to dryness over an electric hot plate (in the hood).

E. *Color Development.*

1. Ten cc. conc. sulphuric acid is added to the residue (D-4) and the color is observed in a test tube when solution is complete. Colorless to light yellow solution is read as negative. Orange to deep orange-brown is read as positive.

RESULTS

Table 1 is a summary of all our results classified according to clinical conditions. Of 39 normal pregnancies, 36 gave a "positive" color reaction. Three cases were interpreted as being negative. In analyzing the three errors, it is found that the color reactions developed were a deep yellow indicating the presence of some pregnandiol, but not sufficient to be considered positive for pregnancy. These tests were performed early in our work before it was realized

[4] Based upon the method for pregnandiol extraction by Astwood and Jones (20) and the color reaction of Talbot et al. (21).

that inadequate neutralization leads to destruction of pregnandiol (see "Technique," Step A-5).

Pregnancy was diagnosed as early as 6 days after a missed period and 21 days after artificial insemination.

The Friedman test was correct in 33 cases. One negative result was recorded 18 days after the calculated date of conception.

Thirty-nine patients complaining of amenorrhea (present for one week to four months), in whom pregnancy was suspected but later ruled out, were tested (table 1). One false positive color reaction was recorded in this group, and this occurred in a woman entering the menopause. The Friedman test gave two false positive reactions. One occurred in a patient who had hypothyroidism and hypoglycemia; the second, in a woman who had had amenorrhea for two months. Comparison of the Friedman and the color tests thus indicates an equivalent degree of accuracy in this series of cases.

TABLE 1. SUMMARY OF RESULTS

Condition	Color Test		Friedman Test	
	Correct	Incorrect	Correct	Incorrect
Normal Pregnancy	36	3	33	1
Amenorrhea (non-preg.)	38	1	29	2
Threatened Abortion	11	0	6	4
Luteal Cyst	0	1	1	0
Hydatid Mole	2	0	0	2
Testicular Tumor	2	0	1	1
Normal Male	9	0	—	—

Total number of cases tested = 103

One of the theoretical objections to the use of pregnandiol determination as a criterion of pregnancy was the possibility of false positive reactions in cases of corpus luteum cysts with amenorrhea. However, no quantitative pregnandiol excretions have been recorded in this condition. One proven case of a corpus luteum cyst was analyzed in this series. The patient, aged 32, entered the hospital complaining of amenorrhea (six weeks) and left lower quadrant pain. Pelvic examination revealed an enlarged uterus and a palpable tumor in the left adrenal region. The tentative diagnosis was ectopic pregnancy. Color reaction of the urine was positive for pregnandiol. The Friedman test was negative. A laparotomy was performed before the Friedman test was completed. A large corpus luteum cyst was found and removed. Two days after operation the color test was negative. Thus, it has been demonstrated that pregnandiol was excreted in a case of corpus luteum cyst and that a false positive reaction may occur with the color test. However, the occurrence of corpus luteum cysts is infrequent and, therefore, is a negligible factor in disturbing the accuracy of the test.

It has been reported that pregnandiol excretion decreases prior to abortion (6, 8, 23). Thus, by following the daily pregnandiol excretion, it was considered possible to predict the course of pregnancy when bleeding occurred. Eleven cases of threatening abortion (table 1) were followed with serial color tests. In four cases the reactions were positive and the prediction was made that pregnancy would progress normally because of normal pregnandiol excretion (*Cases 1, 2, 3, 4*, in table 2). Bleeding stopped shortly after these observations were made. Two cases (*Cases 5* and *6*, table 2), which gave negative color reactions and positive Friedman tests, responded to progesterone therapy.[5] The pregnandiol excretion showed a steady rise and the color test became and remained positive. Pregnancy proceeded uneventfully. One patient had positive color and Friedman tests (*Case 7*, table 2). Four days later, with the onset of bleeding, the color test became negative. A prediction of abnormal pregnancy was made because of the falling level of pregnandiol excretion. The uterus was emptied; an embryo was found but no decidual tissue was obtained. Of three patients who had aborted (1 tubal abortion and two missed abortions, *Cases 8, 9, 10*, table 2), the Friedman test was positive in the three cases and all showed persistently negative color reactions. In one missed abortion (*Case 8*, table 2), there was no excretion of pregnandiol in spite of large doses of progesterone and clinical signs of pregnancy. In *Case 11* (table 2), a prediction of impending abortion was made because of persistent absence of pregnandiol in the urine in the second month of pregnancy. Two weeks later an abortion occurred spontaneously.

[5] Lutocylin generously supplied by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

Although this series of cases of threatening abortion is small, prediction of the course of the pregnancy was made correctly in each case on the basis of the color test. The excretion of chorionic gonadotropin persists while that of pregnandiol seems to respond sensitively to abnormalities in hormonal functions of the embryonic unit. Also, the effectiveness of progesterone therapy is reflected in pregnandiol excretion. The absence of this compound during pregnancy, in spite of large doses of progesterone, seems to indicate a poor prognosis for the pregnancy.

It was postulated that because hydatid mole is similar to chorio-epithelioma pathologically, the excretion of pregnandiol would be low (2, 24). Two cases of hydatid mole were tested (table 1). The color test was negative in each instance and the Friedman, positive.

A high excretion of luteinizing hormone is found in 25 per cent of testicular tumors. Two males with testicular tumors had urine specimens sent to the laboratory for examination. One, with a dysgerminoma, gave a positive Friedman test. The other was negative. Both gave negative color reactions. All normal male urine specimens examined gave negative color reactions (table 1).

TABLE 2. CASES OF ABNORMAL BLEEDING IN PREGNANCY

Case	Age	P.	G.	L.M.P.	Symptoms	Tests[1] Color	Tests[1] Friedman	Treatment	Prediction	Results
No. 1	25	0	1	10/ 2/43	11/27—Bleeding	11/16	+	0	Normal	Normal
						12/ 4	+			
No. 2	32	1	2	12/15/43	3/6—Bleeding severe for 1 day	3/14	+	0	Normal	Normal
No. 3	36	1	2	1/ 1/44	4/2—Abdominal pain and spotting	4/ 5	+	Methyl Testosterone	Normal	Normal
No. 4	28	2	3	2/17/44	4/26—Bleeding	4/26	+	Progesterone	Normal	Normal
						4/27	+			
						4/29	+			
No. 5	21	0	1	Sept. 43	1/21/44—Bleeding	1/22	−	Progesterone	Normal	Normal
						1/23	+			
						1/24	+			
						1/31	+			
No. 6	26	0	2	1/29/44	3/27—Bleeding	3/28	−	Anhydrohydroxyprogesterone	Normal	Normal
						3/29	−			
						3/30	−			
					5/1—Bleeding stopped	4/ 4	+			
						4/ 5	+			
No. 7	31	1	2	1/28/44	3/10—No symptoms	3/10	+	Curettage	Abnormal	No decidua
					3/14—Bleeding	3/14	−			
No. 8	31	0	1	10/ 1/43	12/6—Bleeding-Clots	12/ 9	−	Progesterone	Abnormal	Missed Abortion
						12/24	−			
No. 9	26	0	1	?	1/19—Bleeding	1/19	−	0	Abnormal	Missed Abortion
No. 10	39	2	3	1/29/44	3/1—Bleeding	3/ 6	−	0	Abnormal	Tubal Abortion
No. 11	26	0	1	11/28/43	1/4—Nausea	1/ 4	−	0	Abnormal	Aborted 2/4/44
					1/18—Nausea	1/18	−			

P = Para
G = Gravida
L.M.P. = Last Menstrual Period
[1] The first + in this column refers to the color test and the second + to the Friedman test.

DISCUSSION

The practical advantages of the color test as compared with the Friedman test are summar-

ized in table 3. It may be seen that the color test has several advantages over the Friedman test in that it is more rapid, more specific, economical and does not require animals with attendant housing and feeding facilities. Also factors peculiar to animal reactions—toxicity and refractoriness—are absent in the color test. From the present report, the accuracy of the color reaction compares favorably with the Friedman test. It is obvious that the color reaction requires further and more extensive excretion during the bleeding period increased spontaneously, or in response to progesterone therapy, bleeding stopped and pregnancy proceeded normally. The effectiveness of progesterone therapy can be followed by daily color tests. Failure of pregnandiol excretion to increase from a low level with progesterone seems to indicate an impending abortion.

Conditions which are associated with the excretion of luteinizing hormone, such as hyatid mole and testicular tumors, give posi-

TABLE 3. COMPARISON OF FRIEDMAN TEST WITH THE REPORTED COLOR REACTION FOR PREGNANCY

	Friedman Test	Color Reaction (Pregnandiol)
Rapidity	48 hours	2½–3 hours
Accuracy	70–98%[1]	about 90%[2]
Substance tested for	Chorionic Gonadotropin	Pregnandiol
(a) Specificity	Positive in pregnancy, Hydatid Mole, Chorioepithelioma, testicular tumors.	Positive in pregnancy and corpus luteum cyst
Simplicity		
(a) Specimen	First morning urine 20 cc.	First morning urine 100 cc.
(b) Equipment	Animal Housing and Feeding Facilities	Regular Clinical Laboratory Apparatus
Complications	(a) Toxicity of urine (b) Isolation of animals (c) Refractory animals	(a) Purity of Chemicals
Cost		
(a) Materials	Animals relatively expensive	Chemical reagents very inexpensive
(b) Personnel	Must include care of animals	One technician for 8–12 tests per day

[1] Based upon data in the literature.
[2] This figure is based upon our data and is, of course, subject to revision when a large series will be tested.

testing and it is reported at this time so that other laboratories may submit it to a wider experience than is possible for us under present war-time conditions.

From the data presented, the test is of real value in the rapid diagnosis of pregnancy. However, it may become more important in following cases of bleeding during pregnancy. Because pregnandiol excretion responds to placental changes, the test reflects the state of hormonal function in the placenta. Thus, with the changes in pregnandiol excretion during the period of bleeding, the course of the pregnancy can be predicted. Where pregnandiol was not excreted for long periods of time, pregnancy has ended in abortion in each case of this small series. However, when pregnandiol tive tests for pregnancy by the Friedman technique. However, pregnandiol determination in such cases gives negative results. The test therefore distinguishes between normal placental tissue and abnormal placental or placenta-like tissue.

SUMMARY AND CONCLUSIONS

A three-hour color test for pregnancy, which depends upon the presence of pregnandiol in the urine, is reported. The test is rapid, accurate, specific, economical and requires no animals or special equipment. As a clinical adjunct in cases of threatening abortion, the procedure is a valuable indicator of the course of pregnancy. In cases of hydatid mole and testicular tumor, in which luteinizing hormone is

excreted, the test indicates no excretion of pregnandiol.

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The Protein-Bound Plasma Iodine in Patients with Thyroid Disease

I. Correlation with Basal Heat Production

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SINCE THE demonstration by Kendall (1) and by Harrington (2) that iodine is a part of the molecule of the thyroid hormone, many attempts have been made to correlate the level of the blood iodine with the functional state of the thyroid gland. First efforts (3, 4) to study the blood iodine in this light were faced by the difficulty that there may be considerable inorganic iodine in the normal plasma. This inorganic iodine is, of course, inert hormonally and is subject to a good deal of variability, being greatly increased for a considerable time by the ingestion of even small quantities of iodides in any form, or by contact of the unprotected skin with tincture of iodine.

Therefore, before the determination of the plasma iodine could be of value in the study of thyroid disease, it was necessary to devise a method to eliminate the interference of the inorganic iodine. There are now several procedures available, the most successful being that of Trevorrow and Fashena (5). They precipitate the plasma proteins, which are then washed free of inorganic salts (iodides) by iodine-free distilled water. The concentration of iodine bound to the precipitated protein is then determined. This protein-bound iodine is undoubtedly a closer measure of the hormonal output of the thyroid gland than is the tota plasma iodine. However, Trevorrow believes that not all of the protein-bound iodine (plasma "P" iodine) is hormonal and attempts a further subdivision of it into "T" or thyroxine iodine, and "D" or diiodotyrosine iodine (6). This further separation we have not been able to obtain in this laboratory (7).

However, it is a reasonable supposition that the protein-bound plasma iodine is correlated with the state of activity of the thyroid gland. Previous studies (7–10) have demonstrated that there is at least a rough relationship between the concentration of protein-bound iodine in the plasma and the basal metabolic rate. This is best expressed by the formula of Salter (10) that BMR $\propto$ log (total I$-$3). Although his graph shows considerable scatter of the data about this line, this is to be expected considering the large errors inherent in the determination of small quantities of iodine and in the variability of the basal metabolism.

As a preliminary study on the protein-bound plasma iodine in patients with thyroid disease, the relationship of this iodine fraction to the basal heat production was investigated.

METHODS AND MATERIALS

The protein-bound plasma iodine was determined by the following modification of the method of Trevorrow and Fashena: 15 ml. of

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plasma was added to 100 ml. of distilled water and the proteins were precipitated by the addition of 15 ml. of a 10 per cent aqueous solution of $ZnSO_4$ and 15 ml. of 0.5N NaOH. After mixing and allowing to stand for 15 minutes, the protein precipitate was centrifuged down and the supernatant fluid discarded. The precipitate was then washed several times with 50 ml. portions of iodine-free distilled water, centrifuging the precipitate after each washing and discarding the wash water. Finally, a pinch of ceric sulfate, 15 gm. of iodine-free potassium dichromate and 25 ml. of concentrated H_2SO_4 (dropwise) were added to the precipitate which was then transferred quantitatively to a digestion flask. An additional 50 ml. of concentrated H_2SO_4 and 10 ml. of iodine-free distilled water were added to the flask. The solution was heated to 195°C. and then cooled slowly to 160°C. and rapidly to 60°C. Seventy-five milliliters of iodine-free distilled water was added and, after cooling, 6 ml. of phosphorous acid. The iodine was distilled and titrated in the presence of iodide with a starch indicator as described in the method of Trevorrow and Fashena (5).

Metabolic studies were performed in the Respiration Laboratory of the New York Post-Graduate Medical School and Hospital under the direction of Dr. Cameron V. Bailey. Determinations were made by the open circuit method and the heat production calculated from the respiratory quotient and the composition and volume of the inspired and expired air. The basal metabolic rates were calculated from the normal standard tables of Dubois (11).

FIGURE 1

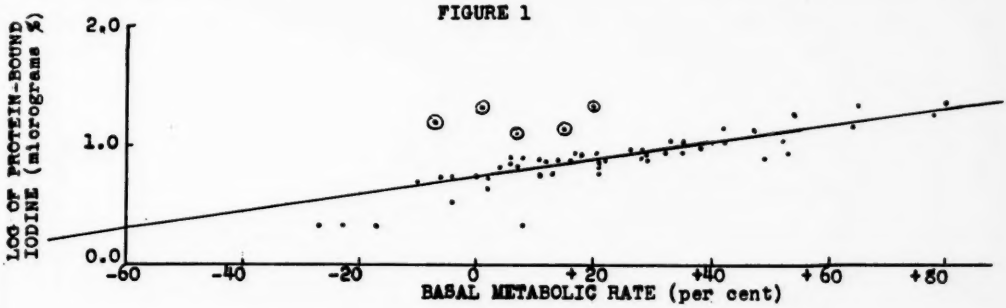
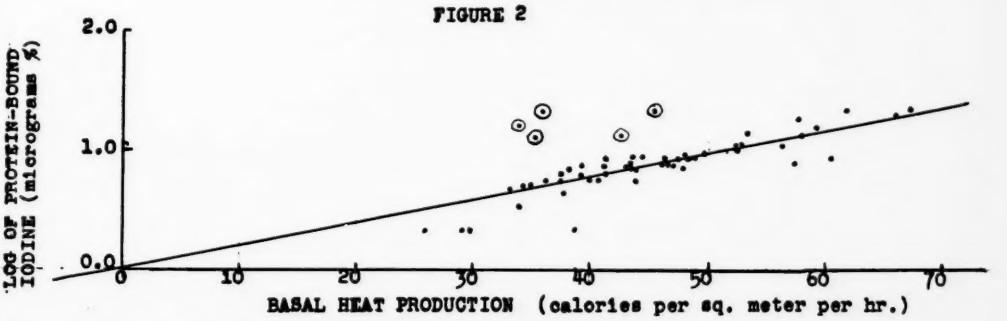


FIGURE 2



Most of the patients studied had toxic goiter, either of the diffuse or the nodular type. The remainder had either no thyroid disease, goiter with a normal basal metabolic rate or hypothyroidism. In 13 of the patients, serial studies were made to follow the effect of thyroidectomy and of the administration of compound solution of iodine (Lugol's solution). Whenever possible, blood was drawn for the iodine determination on the same day that the metabolic study was made, particularly when the metabolic rate was presumed to be changing, as during lugolization or immediately after thyroidectomy. In no case was more than one week allowed to elapse between the estimation of the blood iodine and the basal metabolism.

TABLE 1. THE BASAL HEAT PRODUCTION, BASAL METABOLIC RATE, AND CONCENTRATION OF PROTEIN-BOUND PLASMA IODINE IN PATIENTS WITH AND WITHOUT THYROID DISEASE

No.	Sex	Age	Plasma Iodine (Gamma %)	Basal Metabolic Rate	Determined Basal Heat Production (cal/sq.m/hr.)	Expected Basal Heat Production (cal/sq.m/hr.)	Per Cent Error	Comment
Patients Without Organic Thyroid Disease:								
Pheochromocytoma								
1	F	42	2.1	+ 8	38.9	15.9	59.3	
Paroxysmal Tachycardia (cause unknown) With Cardiac Decompensation								
2	M	40	7.0	+21	47.8	43.6	8.6	
Anxiety State								
3	F	71	5.6	+21	40.0	38.4	4.0	
4	F	27	7.0	+16	42.9	43.6	1.6	
5	F	40	7.3	+29	47.1	44.2	6.1	
Patients With Organic Thyroid Disease:								
Non-Toxic Nodular Goiter								
6	F	49	6.3	+ 4	37.5	41.0	9.3	
			2.1	−27	26.0	15.9	38.8	3 months following thyroidectomy
7	F	34	7.7	+ 8	39.4	45.7	16.0	
Non-Toxic Diffuse Goiter								
8	F	31	5.0	− 6	34.4	35.8	4.1	
			4.8	−10	33.1	34.8	4.8	Following 3 months parenteral administration of thyrotropic hormone
9	F	44	5.6	+13	40.7	38.4	5.6	
Primary Myxedema								
10	F	51	3.2	− 4	34.0	25.8	24.1	On maintenance dose thyroid extract (2 gr. o.d.)
Post-operative myxedema								
11	M	53	7.7	+22	46.1	45.7	0.9	On maintenance dose thyroid extract (1 gr. o.d.)
Toxic Nodular Goiter								
12	F	51	8.4	+18	41.3	47.3	14.4	
13	F	47	8.8	+26	45.3	48.3	6.6	
			5.0	− 4	35.0	35.8	2.3	Following 3 weeks of Lugol's solution orally
			21.1	(+ 1)*	(36.0)*			6 hours following thyroidectomy
			6.8	+ 6	38.2	42.6	10.3	2 months following thyroidectomy
14	F	20	8.4	+21	46.1	47.3	2.6	
Toxic Diffuse Goiter								
15	F	50	7.5	+21	42.3	45.2	6.8	
16	M	49	7.7	+49	57.4	45.7	20.4	Marked anxiety
			6.3	+ 7	41.2	41.0	0.5	2 months following thyroidectomy
17	F	53	7.7	+28	46.7	45.7	2.2	
18	M	28	8.4	+53	60.5	47.3	22.1	Marked anxiety
19	F	34	8.4	+32	48.2	47.3	1.9	
			15.8	− 7	34.1			24 hours following thyroidectomy
20	F	30	8.4	+28	47.3	47.3	0.0	
21	M	56	8.4	+28	48.0	47.3	1.5	
			5.5	0	37.5	37.9	1.1	3 months following thyroidectomy
22	F	44	8.6	+35	48.6	47.9	1.4	
			6.3	+14	41.1	41.0	2.4	Following 1 week of Lugol's solution orally
			2.1	−17	29.8	15.9	46.7	2 months following thyroidectomy
23	F	41	9.8	+38	49.7	51.0	2.5	
24	M	44	10.0	+35	52.2	51.5	1.3	
			7.4	+11	43.0	44.7	3.9	Following 2 weeks of Lugol's solution orally
			6.9	+12	43.5	43.1	0.9	2 months following thyroidectomy
25	M	28	10.5	+33	52.2	52.5	0.6	
			5.6	+11	43.8	38.9	11.1	2 months following thyroidectomy
26	F	29	10.5	+52	56.2	52.5	6.6	Marked anxiety
27	M	37	10.5	+42	52.5	52.5	0.0	
28	M	28	13.2	+47	58.0	57.7	0.5	
29	F	47	15.3	+64	59.1	60.9	3.0	
			5.3	+ 2	36.2	36.9	1.9	2 months following thyroidectomy
30	M	47	18.2	+54	57.7	65.0	12.6	Chinese
			21.1	+65	61.8	68.2	10.4	Following 2 weeks of bed rest
			14.1	+42	53.2	59.3	11.4	Following 2 weeks of Lugol's solution orally

TABLE 1. THE BASAL HEAT PRODUCTION, BASAL METABOLIC RATE, AND CONCENTRATION OF PROTEIN-BOUND PLASMA IODINE IN PATIENTS WITH AND WITHOUT THYROID DISEASE—(*continued*)

No.	Sex	Age	Plasma Iodine (Gamma %)	Basal Metabolic Rate	Determined Basal Heat Production (cal/sq.m/hr.)	Expected Basal Heat Production (cal/sq.m/hr.)	Per Cent Error	Comment
			21.1	+20	45.1			24 hours after thyroidectomy
			8.5	+17	43.4	47.3	9.0	1 month after thyroidectomy
31	F	25	19.6	+78	66.0	66.6	0.9	
			13.3	+15	42.5			24 hours after thyroidectomy
			6.2	+ 2	37.8	31.6	16.4	2 months after thyroidectomy
32	F	29	21.3	+80	67.1	68.7	2.4	
			7.8	+ 6	39.2	45.7	16.6	Following 3 weeks of Lugol's solution orally
			11.4	+ 7	35.3			24 hours after thryoidectomy
			2.1	−23	29.2	15.9	45.5	3 months after thyroidectomy

* Estimated

NOTE: Statistical analysis discloses that the correlation between the basal metabolic rate and the plasma iodine concentration may be best expressed in the equation: BMR = 141 log (I) − 103. A study of the data using this equation shows that the calculation of the basal metabolic rate from the iodine by this equation gives a probable error of ±3.0%. The relation between the basal heat production and the plasma iodine is given by the equation: BHP = 52.3 log (I) − 0.8. Calculation of the basal heat production from the plasma iodine using this expression is attended by a probable error of 0.767 calories per square meter per hour, an error less than 2/3 that involved in the direct calculation of the basal metabolic rate from the plasma iodine. This result is satisfactory inasmuch as the expected probable error, allowing for the uncertainty only in the iodine determinations, is 0.54 calories per square meter per hour.

RESULTS

In table 1 are given the essential data for each of the 32 patients studied.

In figure 1 the basal metabolic rates are plotted against log (I). As may be seen, there is a fair correlation between the two sets of data, confirming previous reports, and similar to the relation observed by Salter (10).

In figure 2 the same log (I) is plotted against the basal heat production in calories per square meter of body surface per hour. This yields a somewhat better correlation. The relation is valid regardless of the state of therapy, the protein-bound plasma iodine declining during lugolization hand-in-hand with the basal heat production, although the total iodine and inorganic iodine in the plasma are obviously greatly increased. After thyroidectomy, the heat production and the concentration of protein-bound plasma iodine both fall to new low levels. The only exception to this rule is that for about 24 hours after thyroidectomy the iodine is considerably elevated over the preoperative level with no corresponding rise in the basal heat production (circled points in figures 1 and 2). The slight tendency of the points to scatter in the direction of increased heat production at high values probably reflects the higher metabolic rate associated with the emotional instability frequently noted in thyrotoxicosis.

DISCUSSION

There is at present no entirely adequate method for the accurate determination of the exact state of activity of the thyroid gland. The basal metabolic rate is notoriously subject to inaccuracy for technical reasons as well as from the effect of non-thyroidal factors (e.g., food, exercise, nutritional status, cardiac status, other endocrine disturbances, etc.). The chemical determinations of the serum cholesterol and the galactose absorption test are also not wholly satisfactory as they, too, are affected by extraneous (non-thyroidal) influ-

TABLE 2. PER CENT ERROR OF BASAL HEAT PRODUCTION CALCULATED FROM PLASMA IODINE BY AGE GROUPS AND SEX

Age Group years	Male %	Female %
WITHOUT HYPERTHYROIDISM		
20–30		1.6
31–40	8.8	8.8
41–50		7.4
over 50	0.9	13.2
WITH HYPERTHYROIDISM		
20–30	8.7	5.4
31–40	0.0	1.9
41–50	8.2	3.2
51–60	2.4	1.6

ences (12). The correlation between the protein-bound plasma iodine concentration and the basal heat production offers a possible method for accurate assay of the state of activity of the thyroid gland. It is the opinion of the authors that in those few cases where a significant difference existed between the iodine level and the basal metabolism, the protein-bound iodine probably represented a closer approximation of thyroid activity than did the basal heat production. When adequately simple and precise methods are available for the determination of the protein-bound plasma iodine, this will probably prove to be a most useful aid in the estimation of thyroid activity. Recently, Riggs, Man and Winkler (13) have noted a similar result after feeding thyroid to myxedematous and to euthyroid patients.

The basal metabolic rate is calculated as a function of the age, sex, and surface area of the patient. It is to be noted from table 2 that the basal heat production is directly correlated to the iodine concentration regardless of age or sex. It is well known that the basal heat production declines with advancing years, and this is presumably due to a reduction in the activity of the thyroid gland with age (14). Consequently, the basal metabolism is calculated on the basis of a standard decrease in thyroid activity with age. However, the protein-bound iodine of the plasma measures directly the activity of the thyroid and should not be expected to decline unless the activity of the thyroid gland also falls off with age. From the limited number of cases in the older age group that were studied and from the statistical relationship emphasized in table 2, the close correlation of the protein-bound plasma iodine with the basal heat production would indicate that the efficiency of the thyroid gland probably decreases with advancing years.

SUMMARY

In a study of 32 patients it was found that the protein-bound iodine of the plasma (plasma "P" iodine) is directly correlated with the basal heat production.

This relationship holds true regardless of age, sex, thyroid disease, lugolization, or thyroidectomy.

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A Case of Probable Pan-Hypopituitarism Following Post-Partum Pituitary Necrosis

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SHEEHAN'S (1) classic description of post-partum pituitary necrosis has introduced a new concept of the pathogenesis of pan-hypopituitarism (Simmonds' disease). This has drawn attention to a possible high incidence of various degrees of this endocrinopathy. That many of these patients may live for long periods of time is evident in Sheehan's case reports as well as in the one that follows. The sequence of events leading up to the failure of the function of the thyroid, the ovaries and the adrenal cortex strongly suggests that the case being reported falls into that category of pan-hypopituitarism which follows post-partum pituitary necrosis.

This report is made to emphasize the fact that, despite the advanced pathology manifested by the patient, suitable organotherapy not only provides symptomatic relief but may materially prolong life expectancy. This therapeutic approach in the management of Simmonds' disease has been successfully applied by others (2, 3).

THE PATIENT

Mrs. S. G. at age of 31 was first examined at this Clinic in 1934 for the complaints of easy fatigability, irritability, amenorrhea, intolerance to cold, partial alopecia and complete loss of body hair, anorexia and diarrhoea. The patient dates her symptoms from 1931, following her second and last pregnancy which was complicated by eclampsia and post-partum hemorrhage necessitating blood transfusion. Lactation failed to appear. The baby survived. The first pregnancy in 1930 was likewise complicated by toxemia and miscarried in the seventh month. After the second pregnancy menses recurred slowly and irregularly for two years with the help of pregnancy-urine extracts; but amenorrhea associated with hot flushes supervened and there was loss of scalp and body hair until only a very sparse growth remained on the head. Libido, which up to that time had been normal, declined sharply. Anorexia and diarrhoea with seven to ten watery stools appeared daily. The body weight remained unchanged at 77 lbs. She developed undue sensitivity to cold.

Her previous health had been relatively uneventful. Her birth weight was only 3½ lbs. She had presented a feeding problem in childhood and remained small in stature throughout. Her weight never exceeded 78 lbs. Her arms and legs were always thinly covered with muscle. She married at age 23 and the first pregnancy followed four years later. In the family history hypertension and goiter were noted but no dwarfism.

Physical examination in 1934, three years after her second and last pregnancy, revealed a dwarfed, under-weight woman whose height was 56 inches and weight 76 pounds. Her skin was dry, thin and mildly sallow. The breasts showed mild atrophy but the vulva and vagina were of castrate type. The face was slightly puffy. The arms and legs were very thin. The musculature was atonic throughout. The blood pressure fluctuated between 85 and 140, systolic and 62 and 84, diastolic. The B.M.R. was minus 29. There was a mild hypochromic anemia. Urinalysis showed a trace of albumin, a few pus cells and hyaline casts.

Following these preliminary observations the

patient failed to return to the clinic until seven years later. During the interval she had received elsewhere a variety of "gland" treatments without much benefit. On return to the clinic in 1941 the patient presented suggestive evidence of Addison's disease, viz., a persistent, faint pigmentation on forehead and

Patient at age of 38; 7 years after post-partum hemorrhage. Height 56 in., weight 66½ lbs.

forearms like a mild tan. The previous symptoms of asthenia, amenorrhea, intolerance to cold, advanced alopecia of scalp and total loss of body hair were now accentuated. Libido was still in abeyance. Her nutritional status was poor because of limited food intake and persistent diarrhoea. The previously noted cachexia was still apparent but chiefly confined to the extremities (see photograph). She was hospitalized for study. There was evidence of widespread endocrinopathy. The skin was atrophic, dry, shiny and faintly pigmented on forehead and forearms. Except for some sparse scalp hair the patient was devoid of hair. Genital atrophy and shrinkage were far advanced. The breasts were still relatively full with a fair amount of gland tissue. Body weight was only 66½ lbs. Blood pressure fluctuated between 110 and 150, systolic and 60 to 70, diastolic. The pulse and temperature were normal. The pertinent laboratory data are given in table 1.

An x-ray plate showed a small sella turcica. Intravenous urography revealed increased intensity of right kidney shadow, suggestive of partial obstruction at the ureteropelvic junction by an aberrant blood vessel.

Since an essentially normal response to the glucose tolerance test was observed in 1941 the insulin tolerance test was attempted to demonstrate the presence or absence of hypoglycemia unresponsiveness. This procedure threw the patient into an Addisonian crisis. Prompt intravenous fluids and 20 cc. of adrenal cortical extract restored the patient. This episode, the low Kepler index and the low values of serum sodium and 17-ketosteroids are amply confirmatory of the adreno-cortical deficiency.

TABLE 1. LABORATORY FINDINGS ON ADMISSION

B.M.R.: fasting, minus 38; 2 hours after protein meal, minus 25.					
Gastric analysis showed low normal acid values.					
Feces revealed neither protozoa nor gross amounts of fatty acids.					
The blood count showed a hypochromic anemia.					
Serum sodium	256 mg. %				
Serum potassium	13 mg. %				
Serum chlorides (as NcCl)	495 mg. %				
Serum cholesterol	403 mg. %				
Serum cholesterol esters	292 mg. %				
Blood NPN	34 mg. %				
Blood Sugar	87 mg. %				
Serum calcium	10.2 mg. %				
Serum phosphorus	4.2 mg. %				
Serum phosphatase	2.5 Bodansky units				
Icterus Index	5.				
Sedimentation rate (Wintrobe)	12 mm. in 8 minutes				
Urea Clearance	60%				
Kepler index (4)	10 (normal 25 or over)				
Urinary 17-ketosteroids (Normal 8–12 mg./24 hrs.)	3.5 mg./24 hours.				
Glucose tolerance	(75 mg. glucose)				
Hours	*F.*[1]	*1*	*2*	*3*	*4*
Mg. glucose per 100 cc. blood	93	130	156	90	94

[1] Fasting.

Thus the clinical diagnosis of pan-hypopituitarism may be said to rest on the evidence of more or less complete failure of the functions of the chief "target" organs, viz., the thyroid, ovaries and adrenal cortex.

Following the study the patient was discharged with the following ambulatory regimen: a) a diet high in protein, caloric and vitamin value, b) substitutional organotherapy in daily dosage of 1) sodium estrone sulfate, 1.25–2.50 mg.; 2) methyl testosterone, 5–10 mg.; 3) thyroid, gr. 0.5–1.0, 4) whole adreno-cortical extract,[1] 2–3 cc. thrice weekly, changed subsequently to desoxycorticosterone acetate[2] in propylene glycol, 0.3–0.5 cc. sublingually.

This therapy in the course of a few months restored a cheerful sense of well-being that the patient had not experienced in ten years. She regained her strength so that she was able to resume the care of her home and family without undue fatigue. Her weight increased to 74 lbs.; general tissue tone improved along with the improvement in nutrition. There was a sharp increase in the growth of the scalp, axillary and pubic hair. There has been almost complete regression in the vaginal atrophy although the uterus remained abnormally small. Withdrawal bleeding has occurred four times in the past three years. Libido has markedly improved. The extremities have shown no striking increase in musculature. The blood pressure has fluctuated between 100 and 140, systolic and 55 and 75, diastolic. The skin has become softer, less atrophic but the faint pigmentation of the forehead and forearm has persisted to date. The myxedema has been dissipated.

Progress: Repeat laboratory observations after 2 years of treatment revealed the following significant data shown in table 2. (Organotherapy was discontinued for the period of the tests—one week.)

TABLE 2. LABORATORY FINDINGS AFTER 2½ YEARS OF TREATMENT

Urinalysis: specific gravity 1.020; occasional pus cells and granular casts.
Urea Clearance: 45%
Blood NPN: 28 mg. %
Blood count: hemoglobin 12 gm. per 100 cc. (71% Sahli), erythrocytes 3,980,000, leucocytes 7,500 and normal differential count.
Hematocrit: 30 volume %
Sedimentation rate (Wintrobe): 12 mm. in 14 minutes.
B.M.R.: minus 3 and plus 1.
Kepler index (4): 13
Insulin tolerance:[1]

Minutes	*(mg. glucose per 100 cc. blood)*
Fasting	123
20	103
30	98
40	90
60	95
90	115
120[2]	109
45	125
60	139

Serum sodium: 266 mg. %
Serum potassium: 19.8 mg. %
Serum calcium: 9.4 mg. %
Serum albumin: 5.5 mg. %
Serum globulin: 3.9 mg. %

[1] 5 units crystalline.
[2] Epinephrine (1-1000) 0.4 cc.

DISCUSSION

Thus from the standpoint of the recent laboratory data the serious component of the syndrome, i.e., the hypoadrenocorticism, remains relatively unchanged. Yet the pluriglandular deficiency symptoms have been largely overcome by the replacement therapy. This is evident not only in the patients relative well-being and usefulness but also by a normal B.M.R., regenerating genital tract, improved nutrition and growth of body and scalp hair. It may be speculated that the absence of a normal electrolyte balance as well as the persistence of abnormal pigmentation indicate a continued severe adrenocortical deficiency. Furthermore, this adrenal defect may be regarded as evidence of failure of the organotherapy to induce any significant regeneration in the damaged anterior hypophysis. In other words, replacement therapy with thyroid and steroid hormones undoubtedly influences body metabolism favorably but it is questionable whether such therapy is followed by any significant permanent recovery of the secretory activity in the involved endocrine apparatus.

The discordant findings of relative hypertension, essentially normal glucose and insulin tolerance curves might be considered incompatible with the diagnosis of Simmonds' disease. However, many of Sheehan's cases showed similar glucose tolerance curves. Hypoglycemia unresponsiveness may be a manifes-

[1] Eschatin, Parke, Davis & Company.
[2] Kindly supplied by Schering Corporation.

tation of a relatively late and untreated phase of the disease. The absence of hypoglycemia unresponsiveness may also be ascribed to a prior pancreatic deficiency, a defect which could prevent typical hypoglycemic reactions. The persistent diarrhoea before organotherapy was instituted might also be explained by a pancreatic lesion or by the adreno-cortical deficiency.

Inasmuch as the systolic blood pressure occasionally attained levels of 150 even before desoxycorticosterone was administered, this relative hypertension was considered incompatible with the adreno-cortical defect. However, the fluctuating character of the pressure may be related to a partial ischemia of the right kidney induced by an obstructive aberrant blood vessel at the uretero-pelvic junction as suggested by intravenous urography. The possibility of a residual nephropathy incident to the two episodes of toxemia complicating both pregnancies must also be considered. The finding of the cellular elements and casts in the urine tend to support these possibilities. It is largely because of this relative hypertension that sublingual administration of desoxycorticosterone was selected instead of pellet implantation.

The appearance of hot flashes early in the patient's menstrual failure might be considered incompatible with the diagnosis of pituitary deficiency. Hot flushes usually imply increased gonadotropic activity of the pituitary as an expression of a failing ovarian function. Yet one cannot dogmatize that a high blood or urinary FSH is an invariable prerequisite to hot flashes. Nor can one regard the pathology of post-partum pituitary necrosis as a static lesion. Sheehan reported variable sequences and transitional changes in his cases, some manifesting spontaneous recovery, while others progressed to more or less complete pituitary failure in the course of months or many years following parturition. In our patient partial failure of the triad of glands—the thyroid, the adrenals and the ovaries—was evident upon first examination in this clinic in 1934, three years post-partum. Relatively complete functional failure supervened in the following seven years. The patient's previous constitutional inferiority may have predisposed her not only to toxemia with both pregnancies but also to the post-partum pituitary necrosis.

The pluriglandular character of the syndrome, the striking genital atrophy and loss of body hair are ample evidence of typical panhypopituitarism. The sequence of events leading up to the endocrinopathy are strongly suggestive of post-partum pituitary necrosis as the most probable cause of the pan-hypopituitarism.

SUMMARY

A case is reported which may be considered a probable example of pan-hypopituitarism resulting from a pregnancy complicated by post-partum hemorrhage. Three years of replacement organotherapy has restored moderate well-being to the patient. However, the persistence of some evidence of adreno-cortical deficiency may indicate a failure of the organotherapy to induce any significant permanent regeneration in the damaged hypophysis.

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Abstracts of
CURRENT ENDOCRINE LITERATURE

Editor: D. A. McGINTY. *Collaborators:* ISRAEL BRAM, RUCKER CLEVELAND, JOHN W. EVERETT, ANNE FORBES, ROBERT B. GREENBLATT, E. C. HAMBLEN, CHARLES W. HOOKER, R. G. HOSKINS, THOMAS H. MCGAVACK, A. E. MEYER, DORIS PHELPS, J. P. PRATT, E. D. REIFENSTEIN, JR., PATRICIA H. SMITH, RUTH ST. JOHN, CHARLES W. TURNER, AND HAROLD WOOSTER.

BOOK REVIEWS

Annual Review of Physiology. Various authors. Am. Physiol. Soc. & Annual Reviews, Inc. Stanford Univ. P. O., Calif. 1944.

This volume contains two articles that are of endocrine interest. F. G. Young of London contributes an authoritative fifty-page article on the "metabolic functions of the endocrine system." Recent literature has been thoroughly mastered and critically epitomized. A notable bibliography (401 references) in which numerous, more specialized reviews are cited is a valuable feature. Not least among the attractive aspects of the article is the author's easy style.

Another interesting article by A. S. Parkes—also of London—on "reproduction and its endocrine control" is mainly restricted to work on mammals and only such clinical reports as present data of general biological interest are considered. Among the topics treated, mention may be made of the sexual cycle in various wild animals—including some remarkable findings in elephants. A section of the biology of ovum and spermatozoön takes up several points that are of interest to stock breeders. The article closes with a discussion of endocrine factors in mammary-gland behavior. A bibliography of 244 citations is appended.—*R.G.H.*

Proceedings of the Conference on Problems of Human Fertility. National Committee on Maternal Health. Edited by Earl T. Engle Banta Publishing Company, Menasha, Wisconsin, 1943. 182 pp.

For the past four years the National Committee on Maternal Health has sponsored annual conferences on human fertility. The Proceedings were originally issued in mimeograph form. The current volume represents papers from recent sessions now made available for wider distribution.

The articles included are: "Endocrine criteria of ovulation"—Elmer L. Sevringhaus; "Embryologic criteria as evidence of ovulation time"—John Rock; "The age of corpora lutea and timing of ovulation"—William W. Greulich; "Electrometric techniques correlated with other studies of ovulation"—John L. Boling; "Some observations on sperm migration through cervical mucus"—Jule K. Lamar; "The transportation and survival of sperm in the vaginal and cervical canals"—Boris B. Rubenstein; "Present problems related to the biology of the vagina"—A. E. Rakoff; "Some observations on the cytology of the trophoblast"—George B. Wislocki; "Placental transmission in relation to the stage of pregnancy"—Franklin P. Snyder; "Placental transmission of radioactive isotopes"—Alfred Gellhorn; "The passage of native proteins through the placenta"—Bret Ratner.

The various papers are freely and informally discussed by members of the Council. The informal style of the presentations is retained in the current volume.

Those interested in the manifold problems of infertility will find in this book a wealth of up-to-date information regarding both what is known and what is not known.—*R.G.H.*

PANCREAS

GOHR, H. AND R. STUDE

Research on the diagnostic value of the blood sugar curve after the oral administration of galactose and dextrose, especially in regard to liver insufficiency, carcinoma, and diabetes mellitus. *Ztschr. f. klin. Med.*, 142: 570. 1943.

The two curves after oral treatment with 50 gm. galactose and 50 gm. dextrose were compared, as well as their usefulness and specificity for the estimation of the liver function.

In cirrhosis of the liver with positive Takata reaction and corresponding greater parenchyma

damage, both curves were raised and protracted. Here the galactose curve shows a somewhat greater rise than the dextrose curve. In the Takata positive, with jaundice, the relationship was similar. In the Takata-negative cases, the galactose curve in several cases showed a rise, while the dextrose curve remained normal.

In diabetes, both curves were naturally protracted and rose sharply. In contrast to the liver patients the dextrose curve rose much higher than the galactose curve. Accordingly, it would seem that the galactose metabolism in the adrenaline-insulin system is not as much affected as the dextrose assimilation.

Also, in cases of carcinoma, there was a partial rise in both curves. In general, the glucose curve rose higher, while in the cases with liver metastasis and positive Takata reaction, the galactose showed a greater rise.—*Courtesy Diabetes Abstracts.*

HANDELSMAN, MILTON B.

Variations in the response of diabetics to Insulin therapy. *New York State J. Med.*, 43: 2287. 1943.

The largest requirements for Insulin and the greatest difficulty in controlling the blood-sugar level are found chiefly in four groups of patients: (1) adolescent diabetics; (2) young adults (under the age of forty at the onset) whose diabetes has progressed rather rapidly, frequently after a mild beginning; (3) patients who were between forty and sixty years of age and thin when the disease manifested itself; and (4) the obese patients (originally mild) who neglected treatment for many years, particularly those who remained obese and had not co-operated in dieting.

In patients over forty who were obese at the onset of the diabetes, normal blood sugars are demanded after a period of treatment, as a criterion of good control. The same rigid standard is demanded and can be attained without complications in all recent cases, whether young or old. However, in others, such as in younger individuals in whom the diabetes has progressed or in "obese middle-aged" diabetics whose disease is of long duration, the blood sugar can be allowed to remain at higher levels and the standards of diabetic control liberalized. In these cases, Insulin will lower excessive hyperglycemia, but an attempt to alter the response of the patient by forcing the blood sugar down leads to the well-known complications of excessive Insulin therapy.—*Courtesy Diabetes Abstracts.*

JOHN, H. J.

Variation and interpretation of glucose tolerance test. *South. M. J.* 36: 624. 1943.

The author recommends the use of a routine 100 gm. dose of glucose rather than one adjusted on a weight basis. A return to normal of the blood sugar within $2\frac{1}{2}$ hours is considered a normal response. It is possible to use the $2\frac{1}{2}$ hour value as a substitute for a complete glucose tolerance test. Hyperglycemia can be produced by a diminished insulogenic function, or by normal insulin secretion blocked by ketosis. The hyperglycemia of obesity and that of diabetes are similar; both can be checked by rigid diet. The end results of a sustained hyperglycemia of any source is a frank diabetes. A non-diabetic patient on a low calorie diet may show a diabetic type curve. On a subsequent normal diet, he is likely to respond with a normal glucose tolerance curve.—*H.A.W.*

JOSLIN, ELLIOTT P.

Medical progress: diabetes mellitus. *New England J. Med.*, 230: 14: 425. 1944.

This is a review article dealing mainly with the use of alloxan in the production of diabetes in experimental animals. The alloxan produces a selective necrosis of the islands of Langerhans of the pancreas. Depending on the dosage of alloxan used a gradual onset of diabetes closely resembling the usual variety found in human beings could be obtained. For instance, in the rabbit 40 mg. per kilogram of body weight was given in repeated intravenous injections.

Of clinical interest was the use of alloxan. A patient with an insulin-producing pancreatic carcinoma had a reduction in the hypoglycemic attacks and in spite of extensive metastasis to the liver the patient gained 35 pounds in weight over a period of 7 months. The symptomatic relief of hypoglycemic attacks obtained through the use of alloxan were only temporary following each series of injections.—*R.B.G.*

KAPLAN, A., C. ENTENMAN AND I. L. CHAIKOFF.

Effects of insulin on the blood lipids of man. *Endocrinol.*, 32: 247. 1943.

The injection of massive doses of insulin into human subjects failed to alter significantly the blood lipid level. The concentration of free and esterified cholesterol, total fatty acids and phospholipids in the blood were unaffected by the almost complete removal of glucose from the blood stream.—*Author's Summary.*

KNOTT, JOHN R., AND JACQUES S. GOTTLIEB

Changes in the electroencephalogram following Insulin shock therapy. *Arch. Neurol. & Psychiat.*, 50: 535. 1943.

Electroencephalographic records were obtained before and after Insulin-shock therapy. Eight of the ten patients exhibited an increase in the alpha index, which was more prominent in the frontal areas.—*Courtesy Diabetes Abstracts.*

LOWELL F. C.

Immunologic studies in insulin resistance. I. Report of a case exhibiting variations in resistance and allergy to insulin. *J. Clin. Investigation*, 23: 225. 1944.

The immunologic behavior of two patients with varying degrees of allergy and resistance to insulin has been studied while both were under treatment with widely varied insulin-dietary regimes. One case is reported in detail. Changes occurred in the resistance to insulin which were clearly related to its withdrawal and administration. When the patients had not received insulin for several months, a responsiveness to its effects was present for a few days after injection was resumed. Following this there was an exacerbation of the glycosuria despite tremendous increases in the amount of insulin given. No "insulin-neutralizing substances" could be detected in the blood of the individual who had not received insulin for several months, but appeared within ten to 12 days after a return of its use. The immunologic nature of insulin resistance in these patients seems clearly proved. The appearance of allergic manifestations in no way paralleled the presence of "insulin-neutralizing substances." A state of allergy was shown to exist when no such substances were in the blood, and at times when the patients were readily controlled either with or without insulin. The author postulates the operation of two immune systems in these individuals: "(1) the allergic mechanism associated with the skin-sensitizing antibody, responsible for generalized urticaria, constriction in the chest, and collapse; and (2) the insulin-neutralizing mechanism associated with a neutralizing antibody for insulin and responsible for the patient's resistance to insulin."—*THMcG.*

LOWELL, F. C.

Immunologic studies in insulin resistance. II. The presence of a neutralizing factor in the blood exhibiting some characteristics of an antibody. *J. Clin. Investigation*, 23: 233. 1944.

The presence of an insulin-neutralizing factor in the blood of two patients clinically resistant to insulin was demonstrated in the following way. After 24 hours' starvation, groups of five mice were each injected intra-abdominally with 0.003 units of insulin, 0.40 ml. or less of patient's serum, and 0.1 ml. or more of saline. This was sufficient insulin to produce symptoms and signs of shock in control animals. The absence of such reactions in the test animals was accepted as evidence for the presence of insulin-neutralizing substances or antibodies. It was found that such neutralizing antibodies disappeared from the sera of patients after six to 12 weeks without insulin and reappeared ten to 12 days after insulin was resumed.—*T.H.McG.*

MILLER, H., D. HURWITZ AND K. KUDER

Fetal and neonatal mortality in pregnancies complicated by diabetes mellitus. *J.A.M.A.* 124: 271. 1944.

An analysis is made from the records of all pregnant diabetic women admitted to the Boston Lying-In, the New Haven Hospital and the New York Hospital for over 10 years. There were 137 mothers observed through 159 pregnancies, compared with 3079 normal mothers. The fetal and neonatal mortality was 29.4% or five times that of the normals. A number of interesting points appear. Abnormally large babies and babies with cardiac hypertrophy and excessive erythropoiesis are significantly more common in diabetic mothers even many years before the onset of the diabetes. These abnormalities however are not related to the high fetal or neonatal mortality. The severity of the diabetes is also not related. Although the high death rate is manifest before the onset of the diabetes and therefore not related to the hyperglycemia, a group of mothers who had glycosuria with an otherwise apparently normal carbohydrate tolerance also had abnormal fetuses. The possible etiologic role of the anterior pituitary is considered.—*A.P.F.*

MIRSKY, I. A., AND W. E. NELSON

Ketosis in relation to the hepatic reserves of glycogen. A study of normal and of diabetic children. *Am J. Dis. Child.* 67: 100. 1944.

The authors have studied the hepatic glycogen reserves in 52 normal and 26 diabetic children following the administration of phlorhizin by a procedure they have described previously (*Endocrinol.* 28: 358. 1941). The test depends on removing sugar from the blood and hence glycogen

from the liver by glycosuria until the liver becomes impoverished of glycogen and hypoglycemia and ketonemia occur. The results are compared with those obtained in normal and diabetic adults. Loss of 15 to 20 grams of sugar had no effect in the normal adult but induced ketonemia in the diabetic adult and in the normal child; loss of even less sugar induced ketonemia in the diabetic child. The reserve of liver glycogen was found to be increased with age and with carbohydrate feeding. The authors conclude that in the presence of infections or other metabolic disturbances children should be given frequent feedings of carbohydrate.—*E.C.R.,Jr.*

PENNOCK, L. L.

Simplification of the treatment of diabetes. *J. Lab. & Clin. Med.* 29. 168. 1944.

The author lays down simple rules for the calculation of dietary and insulin requirements which in his hands have materially simplified the management of the diabetic. The caloric equivalent to be used is calculated from the standard or normal body weight of the individual. Twenty-five to 40 calories per kilogram is used, depending upon the activity of the patient. Two-thirds gram of protein per kilogram of body weight is allowed for women and one gram for men. Fat is kept between 70 and 90 grams per day. The necessary carbohydrate to complete the daily caloric ration is determined by subtraction. From the standpoint of insulin therapy, the author divides his cases into "mild"—demanding no insulin; "moderate"—requiring up to 40 units daily; and "severe"—needing more than 40 units. In the initial prescription the patient is given one unit of insulin for every two grams of sugar excreted in the urine for a 24-hour period. However, no insulin is administered at first if glycosuria does not exceed 20 grams daily. All patients requiring insulin are started on protamine zinc, but in the majority of cases, some unmodified insulin has been added to the regime sooner or later. The author injects this in the same syringe with the protamine zinc. In all cases taking protamine zinc insulin, a small meal is prescribed for bedtime consumption.—*T.H. McG.*

ROSENBAUM, J. D., H. DEKRUIF, AND P. H. LAVIETES

The effect of insulin on the glucose tolerance of normal man. *J. Clin. Invest.* 23: 45. 1944.

The authors served as the subjects of their experiments. They were maintained on constant diets which included the use each morning of a test meal of 50 grams of glucose. The following determinations were made daily throughout a control, an insulin, and a post-insulin period of study: blood sugar in the post-absorptive state and at 90 and/or 120 minutes after the ingestion of the test meal; respiratory quotient in the post-absorptive state, and at 50 and 80 minutes following the ingestion of glucose. Protamine zinc insulin was given in doses varying from 15 to 30 units daily administered in the mid-afternoon; and crystalline insulin was given 15 units at 10:15 A.M. and a like amount at 5:45 P.M. Under the conditions of the experiments, small doses of insulin resulted in excessive hyperglycemia and a delayed rise of respiratory quotient after the ingestion of glucose. Both effects were usually evident within 24 hours of the beginning of insulin administration. In both instances the action was reversible, this change occurring more promptly with regard to the oxidation than to the hyperglycemia. If extra feedings were given at bedtime, they decreased or prevented the loss of tolerance to sugar on the following morning. The authors suggested some analogies between these observations and those well-known reactions of "starvation diabetes."—*T.H.McG.*

RUDY, A., S. B. BEASER AND A. M. SELIGMAN

Vitamin therapy in increased capillary fragility of diabetes mellitus. *Arch. Int. Med.* 73: 23. 1944.

A review of the literature on the clinical use of vitamin P reveals that various forms of vitamin P have been used, but with no clear notion as to what component of citrin was being tested. Such therapy was studied in a wide variety of cases with increased capillary fragility irrespective of the underlying disease, which was frequently a self-limited condition. Conclusions of doubtful validity were drawn in some cases when the criterion of therapeutic effectiveness was clinical bleeding or the result of a negative pressure test for determining capillary fragility. The effectiveness of oral administration of vitamin C and the B complex on the increased capillary fragility in diabetic patients with and without retinitis has been tested, with negative results. The effectiveness of both orally and parenterally administered vitamin P in some patients of this group was studied. Both the hesperidin and the eriodictyol fraction of vitamin P were tested in-

travenously, separately and combined, with negative results. A similar study of the effect of vitamin P therapy on the increased capillary fragility of thrombopenic purpura and rheumatoid arthritis was made, with negative results.—*Authors' abstract.—I.E.*

SCHNETZ, HERMANN

Diabetes mellitus and the disturbance of the external pancreas secretion in biliary disease. *Ztschr. f. klin. Med.*, 142: 512. 1943.

In order to clarify the question of the occurrence and cause of the relationship between disease of the bile duct and diabetes mellitus in the simultaneous disturbance of the external pancreas secretion, improved clinical function tests for the internal and external pancreas secretions were developed. In seventy-six cases, partly from the clinical and roentgen findings and partly from only latent bile-duct illness, latent diabetic metabolic disturbance had already very plausibly been diagnosed from the clinical symptoms. In forty-five cases, the detection of a simultaneous disturbance of the external and internal pancreas secretion was made possible with the help of the combined function test and was in complete agreement with the clinical findings.

In the train of bile-duct disease and pancreas diabetes, there likewise appear hypovitaminoses (vitamin B and vitamin C deficiency symptoms).

The simultaneous appearance of diseases of several upper-abdominal organs (bile duct—gastroduodenum—pancreas) can be traced back to the organic and functional disturbances of the work-cycles of the upper-abdominal organs because of their close anatomic association and the intimate functional connection of the associated organs.—*Courtesy Diabetes Abstracts.*

STOCKS, P.

Diabetes mortality in 1861–1942 and some of the factors affecting it. *J. Hyg.*, 43: 242. 1944.

The chief factors affecting diabetes mortality rates were increased reporting on death certificates, earlier detection and detection of lesser degrees of illness, food rationing, increased sugar consumption, and introduction of insulin treatment. The rise in rates of the last century had ceased before the sugar shortage of 1915–19. A marked change in sex ratio with greater decreases in incidence among males was reported in Europe, New Zealand, and the U.S., as well as in Great Britain. The introduction of insulin therapy caused a marked fall in rates among persons under 64. The introduction of food rationing also decreased rates. Severe conditions in the winter quarters of 1940 and 1941 appeared to hasten deaths of the chronically ill, including diabetics, and a slight rise in rates occurred followed by a decline attributed to food rationing.—*H. D. Vera (Biol. Absts.)*

TOLSTOI, E.

Newer concepts in the treatment of diabetes mellitus with protamine insulin. *Am. J. Digest. Dis.*, 10: 247. 1943.

Criteria are presented for the satisfactory treatment of diabetes mellitus when using protamine insulin, and the details of the method used in the outpatient department at the hospital are described. The basic principle was the quantity of glucose utilized and not excreted, and the evidences for such utilization were maintenance of optimal weight, absence of diabetic symptoms, and absence of urinary ketones.

The complications attributable to hyperglycemia and glycosuria are discussed, and the author believes that the evidence for such assumptions is inferential and inconclusive. To quote: "Therefore, we have not insisted on a normal blood sugar and a sugar-free urine, as our experience over a five-year period has led us to the conclusion that such rigid demands are not necessary. Our patients treated with protamine insulin, in spite of the constant glycosuria, were socially and economically useful. They developed no more frequent nor more severe infections, and, when surgical measures were required, their wounds healed as readily as normals. When, however, we tried to adjust the glycosuria too finely or maintain the urine free from sugar, unpredictable and disconcerting reactions occurred."—*Courtesy Diabetes Abstracts.*

PARATHYROIDS

BYRON, C. S., AND S. MICHALOVER

Calcinosis and scleroderma with parathyroidectomy. *Ann. Int. Med.* 18: 225. 1943.

A woman 24 years of age presented calcinosis universalis, scleroderma, sclerodactylia and muscle atrophy. The calcium metabolism was normal but there was a tendency toward a negative phosphorus balance. Hemithyroidectomy and the removal of two parathyroids had little influence on the clinical course and no effect on the calcium deposits.—*M.B.G.*

REID, M. R., AND J. RANSCHOFF

Intravascular parathyroid grafts. *Am. J. Med. Sci.* 206: 731. 1943.

The authors have devised a method of grafting by producing pulmonary infarcts with small fragments of parathyroid tissue injected into the external jugular veins of dogs rendered deficient in parathyroid hormone by total parathyroidectomy. The animals were maintained on 1 grain of thyroid daily, since they were thyroidectomized in removing the parathyroid glands. Symptoms of tetany in these animals were relieved by the intravenous injection of 10 cc. calcium gluconate and 1 cc. parathormone. Eleven dogs were given iso-grafts. Of these, 3 lived until sacrificed at 5, 6 and 7 months respectively; the other 8 died of tetany while unobserved during the night (bitten tongues, upset food pans, and distorted positions being considered as evidence of a tetanic death). The authors believe that many more of the animals would have been carried to complete recovery if it had been possible to provide 24-hour nursing care. All of the animals showed a diminution in the number of attacks of tetany during the second 2 postoperative weeks as compared with the first 2; the surviving animals had normal blood chemical findings at the time of sacrifice. A second group of 12 dogs were given cross-grafts. Of these, one lived 3 months, and 4 for over a month postoperatively. These animals showed the same phenomenon of decreasing frequency of tetany, but after about 3 to 5 weeks they exhibited again a rise in the frequency of tetany until at the time of their deaths, they needed calcium and parathormone almost daily. None of the dogs had any pulmonary signs or symptoms from the parathyroid infarcts. At postmortem, masses resembling parathyroid tissue were found in the lungs of two animals. The authors point out that a physiologic need on the part of the host must be present if the grafted tissue is to function. They contend that this method enables one to graft tissue into a very vascular bed of loose structure with a minimal degree of postoperative hemorrhage. They suggest that when an adequate source of properly prepared and acclimated tissue for cross-grafting (such as stock tissue cultures grown in pooled human plasma) become available, the method would have clinical applicability because it would lend itself to repeated grafting attempts until successful takes were achieved, repeated attempts with only a small degree of operative trauma and an unlimited implantation site.—*E.C.R.,Jr.*

THYMUS

NELLEN, MAURICE

Thymectomy for myasthenia gravis. *Brit. Med. J.* 2: 778. 1943.

The report of a case is recorded in which thymectomy for myasthenia was done with successful results. The operation was performed on a 23-year-old nurse. Histologically the thymus was found to contain hyperplastic lymphoid tissue.—*R.B.G.*

THYROID

BARNES, C. G., AND E. J. KING

Galactose tolerance tests in thyrotoxicosis. *Quart. J. Med.* 12: 128. 1943.

Forty patients with thyrotoxicosis were given oral galactose tolerance tests; intravenous galactose tolerance tests were made on twenty-two patients. Normal intravenous tests with abnormal oral tests were obtained, and the authors suggest that the latter finding may be the result of abnormally rapid absorption of the sugar. The value of the oral tests in the diagnosis of early thyrotoxicosis is discussed.—*P.H.S.*

DAVIS, C. H.

Hypothyroidism as a problem in women. *Am. J. Obst. and Gynec.* 46: 85. 1943.

The author presents statistics of his personal experiences with basal metabolic determinations in women of Milwaukee, Wisconsin and Wilmington, Delaware. On the basis of these statistics he believes that there is as much thyroid problem in Delaware as in Wisconsin and that there has been a decrease in hyperthyroidism and an increase in hypothyroidism during the last two decades.

A plea is made for the routine use of iodine and thyroid substance in the treatment of hypometabolic pregnant women since the author reports only one instance of an enlarged thyroid at birth in over 1,500 deliveries.—*E.C.H.*

FLEISCHMANN, W., H. B. SHUMACKER, JR., AND W. L. STRAUS, JR.

Influence of age on the effect of thyroidectomy in the rhesus monkey. *Endocrinol.*, 32: 238. 1943.

In 6 adult rhesus monkeys total thyroidectomy had no effect on their appearance, activity or serum cholesterol level. In two of these animals, the B.M.R. was estimated before and after re

moval of the thyroid and showed no change. The animals survived the thyroidectomy from 44 to 487 days. The completeness of the thyroidectomy was demonstrated both by anatomic search and by physiologic tests with thyrotropin. In addition, two infant rhesus monkeys were thyroidectomized at the age of about 8 months. Both animals showed a sharp rise of serum cholesterol following thyroidectomy. The level of serum cholesterol in the longer surviving infant monkey reached a peak of 326 mg. per cent 5 weeks after operation. Complete cessation of growth also was observed in this animal. These data suggest that the age factor is of great importance in determining the effect of thyroidectomy in the rhesus monkey.—*Author's Summary.*

GORDEN, G., M. H. SOLEY, AND F. L. CHAMBERLAIN

Electrocardiographic features associated with hyperthyroidism. *Arch. Int. Med.*, 73: 148. 1944.

The authors report studies on 168 patients for whom electrocardiograms were taken during the period of thyrotoxicosis. The noteworthy electrocardiographic findings in order of frequency were: (1) sinus tachycardia; (2) various abnormalities of the T waves, of which low amplitude and notching were the most common; (3) auricular fibrillation; (4) partial auriculoventricular block, and (5) in rare instances auricular flutter. After exclusion of other causes for electrocardiographic abnormalities, the incidence of these findings was the same for the younger (14 to 40 years) and for the older (41 to 75 years) group of patients. After treatment of hyperthyroidism, the abnormalities tend to disappear. In the presence of hyperthyroidism, electrocardiograms must be interpreted with caution, since they may simulate those of persons with organic heart disease.—*Authors' Abstract—I.B.*

JACOBS, J. E.

Osteodystrophia fibrosa cystica and juvenile hyperthyroidism. *South. M. J.* 36: 668. 1944.

Two cases of juvenile hyperthyroidism that showed osteodystrophia fibrosa cystica with diffuse osteoporosis complicated by pathologic fractures are presented. One case is well three years after thyroidectomy. The other unoperated case is still toxic, with the above signs. Normal values for serum calcium and phosphorus excluded the differential diagnosis of hyperparathyroidism.—*H.A.W.*

LIKOFF, W. B., AND S. A. LEVINE

Thyrotoxicosis as the sole cause of heart failure. *Am. J. Med. Sci.* 206: 425. 1943.

A study was made of 409 cases of thyrotoxicosis operated upon at the Peter Bent Brigham Hospital (Boston) from 1923 to 1941, inclusive. There were 331 (81%) "non-cardiacs" and 78 (19%) "cardiacs." Among the latter there were 45 with hypertensive disease, 20 with rheumatic heart disease, 12 with coronary artery disease, and one with syphilitic aortic insufficiency. There were 39 cases of heart failure among the 78 "cardiacs" (50%), and 21 instances of definite congestive failure among the 331 "non-cardiacs" (6.3%). It is apparent, therefore, that thyrotoxicosis not infrequently is the sole cause of congestive heart failure. It was found that congestive failure was more likely to occur in the female sex, with increasing age, when the thyrotoxic state lasted longer, and when auricular fibrillation was present. No satisfactory explanation was found for the heart failure especially in the "noncardiac" group. It is suggested that vitamin B deficiency may play a contributory part. The similarity between symptoms and physical findings in mitral stenosis and thyrotoxicosis may lead to errors in diagnosis, for even left auricular dilatation on roentgen ray examination is found in the latter condition. In 99 cases with cardiac involvement there was no surgical mortality. All but 7 of these had a one-stage subtotal thyroidectomy. The surgical mortality in 310 cases without heart disease, however, was 2.6%. They, therefore, do not believe that the so-called severe thyrocardiacs require a multiple stage operation, and feel that these cases cause less concern than the younger exophthalmic goiter when surgical treatment is planned. It is evident that "masked thyrotoxicosis" is being overlooked as a cause of heart failure, an error which is very costly because the condition is curable.—*Authors' Summary.*

MEANS, J. H.

The nature of Graves' disease with special reference to its ophthalmic components. *Am. J. Med. Sci.* 207: 1. 1944.

The author reviews the pertinent observations in the literature and correlates them with the findings of his own group, which includes Rawson, Hertz, Lerman, and Galli-Mainini. He divides Graves' disease into: a) the *classic type*, with both toxic goiter and certain peculiar ophthalmic manifestations, and b) the *special ophthalmopathic*

type, with characteristic ophthalmic involvement but little or no accompanying thyrotoxicosis, (there may even be hypothyroidism). In the former, the degree of eye involvement parallels the amount of thyroid toxicity; in the latter, the eye involvement and the thyroid toxicity are disassociated. The indications for therapy are based on the state of the thyroid in the former, and on the state of the eyes in the latter. The author points out that a sharp line can not be drawn between these types in all cases, but emphasizes that there are cases, or stages in cases, where the subdivision can be made with ease.

From the point of view of *etiology*, the malady is determined in part by inherited constitution to which is added some environmentally imposed stress. The *onset and course* of Graves' disease are most variable. It may start with either thyrotoxic manifestations or ophthalmic, or with the two simultaneously. The onset may be abrupt or gradual. There may be one or more spontaneous remissions. There is a definite tendency for the disease to be self-limited. The total duration may be only months, or it may be, if untreated, many years. It may occur in either sex and at any age. Sometimes it goes into a low grade, chronic form.

The *ophthalmic manifestations* include: wild, staring appearance; exophthalmos; retraction of the upper lid; lid lag; widening of the palpebral slits and infrequent winking; lack of near convergence; pigmentation of eyelids; globe lag; absence of brow wrinkling; edema of eyelids; chemosis or edema of the global conjunctiva; ulceration of the cornea; epiphora; and visual defects such as diplopia, diminution of visual acuity and bitemporal hemianopsia (1 case). These various signs are of importance only to determine: a) whether the patient has any ophthalmic involvement; and b) whether the eye lesion is advancing, regressing, or remaining stationary. Edema of the lids, chemosis and injection of the conjunctiva are thought to indicate a progressing process and the absence of them an inactive or receding condition. The ophthalmic signs may be asymmetric, as in the case of lid retraction, but they are rarely completely unilateral. The finding of bilateral eye signs of the Graves' variety is overwhelming evidence in favor of that diagnosis. Other conditions with bilateral exophthalmus encountered by the author include skull deformities with shallow orbits, such as oxycephaly, Hand-Schuller-Christian's disease, rarely myasthenia gravis, and possible certain hypertensions. When Graves' disease of the classic type is treated with partial thyroidectomy, the exophthalmos appears to subside but it seldom completely disappears. However, in the special ophthalmopathic type, the eye condition becomes aggravated after operation, and the progress of the lesion frequently justifies the term 'malignant exophthalmos'; orbital decompression is sometimes necessary to save the eye. With very few exceptions, it is the post-thyroidectomy cases in which such serious eye conditions develop. If there is any hint before thyroidectomy has been done that the opthalmopathy may become malignant the removal of the thyroid is contraindicated.

The *pathologic physiology of the ophthalmic component* has been constructed upon two findings: a) an increased tissue pressure from the tendency to water retention which results in swelling of the extraglobal orbital contents especially the extrinsic muscles, and b) weakness of the muscles with decreased back pull. It is postulated that the sequence of events in exophthalmogenesis is as follows: 1) the muscles are weakened and lose tension; 2) the eyeball is forced forward by the increased tissue pressure; 3) the tissue pressure falls as the globe moves forward; 4) fluid passes from the capillaries to the tissues until a new equilibrium is reached with the muscles stretched and the globe protruding; 5) if this situation is stabilized, permanent inactive residual exophthalmos results; 6) if this situation is unstable, the process is repeated; 7) ultimately, the weakened muscles cannot withstand the tissue pressure and in turn become edematous, as do the lids and surrounding tissues; progressive malignant exophthalmos results. Considerable evidence supports the view that an excess of thyrotropic hormone has something to do with the ophthalmic pathogenesis, as indicated below, but the relationship is not a simple one.

The author postulates that the sequence of events in the *morbid physiology of the classic type* is as follows: 1) the anterior pituitary gland, perhaps because of a nervous impact reaching it via the hypothalamus, secretes excess thyroid-stimulating-hormone (TSH); 2) the excess TSH a) stimulates the thyroid gland to become hyperplastic, and b) at the same time causes some increase in the volume of the extraglobal orbital contents; 3) the hyperplastic thyroid a) exhibits an increased avidity for iodine, b) has an increased power to inactivate TSH, and c) produces an excess thyroid hormone; 4) the excess thyroid hormone a) usually, but not always, produces hyperthyroidism, and b) inhibits the production of TSH by the anterior pituitary; and 5) in the process of stimulating the thyroid gland the excess TSH a) is inactivated, and b) appears

in the urine as excess inactivated TSH (Rawson has shown it can be reactivated by heating the urine).

The sequence of events in the *morbid physiology of the ophthalmopathic type* is thought to be as follows: 1) this is the same as in the classic type; 2) the excess TSH a) fails to invoke in the thyroid gland (for reasons unknown) the same degree of response as in the classic type, but b) induces the same increase in the volume of the extraglobal orbital contents as in the classic type; 3) the poorly responsive thyroid gland fails a) to inactivate TSH, and b) to produce excess thyroid hormone; 4) lack of excess thyroid hormone a) prevents the production of hyperthyroidism, and b) removes the inhibition to anterior pituitary TSH production, which, therefore, increases still more; and 5) the excess TSH- a) is not inactivated, b) aggravates the ophthalmic situation, and c) is excreted in its active, as well as its inactive form in the urine. The relationship (described by Marine) of the gonad to the pathogenesis of the ophthalmic component remains to be correlated with this sequence.

The author stresses the necessity of keeping the morbid mechanism of the disease in mind in planning treatment, and of recognizing that subtotal thyroidectomy may be very helpful to some patients and very harmful to others.—*E.C.R.,Jr.*

PAUL, J. T., L. R. LIMARZI, AND L. SEED

The effect of myxedema upon hemopoiesis in leukemia and related disorders. *Am. J. Med. Sci.* 206: 625. 1943.

Total thyroidectomies were performed on one patient with polycythemia vera, three patients with erythroleukemia, one patient with chronic myeloid leukemia, and one patient with chronic leukemia. A complete hematologic survey including sternal bone marrow examination, the basal metabolic rate, blood volume estimations, and blood chemistry including cholesterol, calcium, phosphorus, serum proteins and uric acid was made in each case prior to and after the removal of the thyroid. The myxedematous state was judged by the development of dry, coarse skin, puffiness, heat intolerance, depressed basal metabolic rate and elevated blood cholesterol. The authors concluded: 1) Erythropoiesis is depressed in polycythemia vera after a total thyroidectomy and development of myxedema. The anemia is macrocytic and hyperchromic in type. Leukopoiesis is unaffected. 2) In erythroleukemia myxedema induced a moderate to marked depression in erythropoiesis. The anemia is macrocytic or microcytic in type. There is stimulation of leukopoiesis. In 1 case, after thyroidectomy there was early a "megakaryocytic crisis" followed later by normal platelet counts. 3) Hemopoiesis in chronic lymphatic and chronic myeloid leukemia is not altered by an induced myxedema.—*E.C.R.,Jr.*

SOFFER, L. J., C. COHN, GERSON LESNICK, H. SOBOTKA, AND M. JACOBS

Effect of sodium iodide, magnesium sulfate, thyroxin, and thyrotropic hormone on the blood magnesium partition. *J. Clin. Investigation.* 23: 263. 1944.

The total and bound fractions of blood magnesium were studied in normal dogs following the prolonged intravenous administration of sodium iodide, 0.5 gms. daily for 31 to 35 days, and of magnesium sulfate, 3 cc. of a 25 per cent solution daily for from 42 to 75 days. Similar studies were made following the subcutaneous injection of 4 mgm. of thyroxin daily for from 27 to 30 days; and of 100 to 500 guinea pig units of thyrotropic hormone daily for from 16 to 34 days. Magnesium sulfate, sodium iodide, and thyroxin did not appreciably influence the total blood magnesium nor the percentage of the bound fraction. Injections of thyrotropic hormone did not significantly alter the total blood magnesium but at first increased the percentage of the bound fraction with a later reduction "to levels considerably below the control values." The authors suggest that the initial increase in bound magnesium after thyrotropic hormone is similar in kind and degree to that seen in human Graves' disease. They believe the later fall to levels "seen only in myxedema in the human" may be explained by the development of an antithyrotropic hormone, as in one instance hypophysectomy was observed to abolish this effect. The failure of thyroxin to alter bound magnesium of the blood is "in harmony with the clinical impresssion that hyperthyroidism due to thyroid administration is not identical with Graves' disease."—*T.H. McG.*

WILLIAMS, R. D., AND E. C. KENDALL

Influence of thiamine on induced hyperthyroidism. *Arch. Int. Med.* 72: 185. 1943.

Two physically healthy women, maintained continuously on a basal diet providing only 0.22 mg. of thiamine per 1000 calories but adequate in all other respects, received large doses of desic-

cated thyroid gland (subject 1, 0.6 gm. per day; subject 2, 0.5 gm.) for 241 days. Besides the periods of preliminary and subsequent observation the study was divided into 3 periods. Thiamine hydrochloride was liberally provided during the first period of 22 days; it was restricted to 0.45 mg. per day during the second period of 136 days; it was provided in increasing amounts during the third period of 81 days. The basal metabolic rate of each subject rose to approximately plus 25 per cent during the initial period of administration of thiamine and desiccated thyroid. It fell to minus 8 per cent and plus 11 per cent, respectively, during the period of restriction of thiamine, but rose to approximately plus 25 and plus 30 per cent, respectively, in the third period, when thiamine hydrochloride was again provided. Throughout the period of administration of desiccated thyroid the concentrations of pyruvic acid and lactic acid in the blood after administration of dextrose were high, but they were higher during the period of restriction of thiamine. The conclusion appears justified that the thyroid hormone is less effective in promoting the metabolic activity of the organism in a state of thiamine deficiency. The results of this study may be interpreted as additional evidence that the function of the thyroid hormone is primarily to mobilize metabolites for oxidation by enzyme systems of the organism and only indirectly to increase the rate of oxidative processes.—*Authors' Summary and Conclusions.—I.B.*

WILLIAMS, R. H., B. J. JANDORF, AND G. A. KAY

Methods for the determination of thiouracil in tissues and body fluids. *J. Lab. & Clin. Med.*, 29: 329. 1944.

The methods chosen for the determination of thiouracil in body tissues and fluids are based on the fact that the N—C—N linkage of thiouracil reacts with sodium nitroferricyanide in alkaline solution giving a greenish color which can be quantitated in a colorimeter. Grote's reagent, as prepared by the authors, remains stable for two weeks or more if kept at ice-box temperatures. Hydroxylamine hydrochloride is the only component of the reagent in which they have thus far observed deterioration. The authors describe variations for the adaptation of their method to the analysis of urine, blood, and tissues. In estimating blood levels, it was found that recovery was not complete unless the assay was preceded by tryptic digestion for the purpose of releasing a portion of the thiouracil routinely observed to be bound by proteins. From 91 to 100 per cent recovery of added thiouracil has been possible; the majority of the authors' determinations lie close to the 100 per cent figure. The particular color reaction obtained with thiouracil has not been duplicated, even by other substances with the C=S linkage such as sodium thiocyanate and thiosulfate, cysteine, cystine, glutathione, methionine, thiamine, and sulfanilamide.—*T H.McG.*